COURTNEY M. PRICE
VICE PRESIDENT
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American Chemistry Council
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December 13, 2001

Via US Mail and e-mail

Christine Todd Whitman, Administrator
U.S. Environmental Protection Agency (EPA)
P.O. Box 1473
Merrifield, VA 22116

Re: Rubber and Plastic Additives (RAPA) Panel, Consortium No.
HPV Chemical Challenge Program Submission
Substituted p-Phenylenediamines (PPD) Category
Category Justification and Testing Rationale

Dear Governor Whitman:

The RAPA Panel of the American Chemistry Council is pleased to submit the subject documents to EPA's HPV Chemical Challenge Program (Program) as our test plan for a category covering five of the 39 chemicals RAPA is voluntarily sponsoring in the Program. The RAPA Panel includes the following member companies: Bayer Corporation, Ciba Specialty Chemicals Corporation, Crompton Corporation, Flexsys America L.P., The Goodyear Tire & Rubber Company, The Lubrizol Corporation, Noveon, Inc., R.T. Vanderbilt Company, Inc., and UOP, LLC.

In this submission, please find the *Category Justification and Testing Rationale* for the category *Substituted p-Phenylenediamines*. Five chemicals in the category are sponsored in the Program, as listed in the following table:

RAPA Panel Substituted p-Phenylenediamine Category Chemicals Sponsored in the U.S. HPV Chemical Challenge Program	
CAS Number	Compound Name
101-96-2	p-Phenylenediamine, N,N-di-sec-butyl
3081-14-9	p-Phenylenediamine, N,N-bis(1,4-dimethylpentyl)
68953-84-4	1,4-Benzenediamine, N,N'-mixed Ph and toyl derivatives
3081-01-4	p-Phenylenediamine, N-(1,4-dimethylpentyl) N'-phenyl
15233-47-3	p-Phenylenediamine, N,(1-methylheptyl)-N'-phenyl,

Data for two additional chemicals in the category, listed in the table below, are used to support the conclusions reached for the category.

RAPA Panel Substituted pPhenylenediamines Category Additional Chemicals in the Category	
CAS Number	Compound Name
[illegible]	p-Phenylenediamine, N-Isopropyl-N'-phenyl-,
[illegible]	p-Phenylenediamine, N-(1,3-dimethylbutyl) N'-phenyl

In addition to the *Category Justification and Testing Rationale*, please also find attached robust summaries contained in IUCLID-formatted documents for each of the five sponsored chemicals and the two supporting chemicals in the category.

This submission is also being sent electronically to the following e-mail addresses:

Oppt.ncic@epa.gov
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If you require additional information, please contact the RAPA Panel's technical contact, Dr. Anne P. LeHuray at (703) 741-5630 or *anne_lehuray@americanchemistry.com*.

Sincerely yours,

Courtney M. Price
Vice President, CHEMSTAR

Attachments

Cc: C. Auer, EPA/OPPT
B. Leczynski, EPA/OPPT
RAPA Panel (without attachments)
S. Russell, ACC (without attachments)

AR201-13383A

Substituted p-Phenylenediamines Category Justification and Testing Rationale

CAS Nos. 101-96-2, 3081-14-9, 3081-01-4, 15233-47-3, and 68953-84-4
(+ SIDS Chemicals 101-72-4 and 793-24-8 for data purposes)
Rubber and Plastic Additives Panel
American Chemistry Council
December 2001

List of Member Companies in the Rubber and Plastic Additives Panel

The Rubber and Plastic Additives Panel of the American Chemistry Council include the following member companies: Bayer Corporation, Ciba Specialty Chemicals Corporation, Crompton Corporation, Flexsys America L.P., The Goodyear Tire & Rubber Company, The Lubrizol Corporation, Noveon, Inc., R.T. Vanderbilt Company, Inc., and UOP, LLC.

Executive Summary

The American Chemistry Council's Rubber and Plastic Additives Panel (RAPA), and its member companies, hereby submit for review and public comment their test plan for the Substituted p-Phenylene diamines category of chemicals under the Environmental Protection Agency's High Production Volume (HPV) Challenge Program.

As discussed in the report that follows, Substituted p-Phenylenediamines (PPD), which are used as antidegradants in rubber, fuel additives, or in monomer distillation, are defined as phenylenediamines with various substitutions. These uses require stability at high temperatures, low biodegradation and very low water solubility and low vapor pressure. In consideration of animal welfare concerns to minimize the use of animals in the testing of chemicals, the Panel has conducted a thorough literature search for all available data, published and unpublished. It has also performed an analysis of the adequacy of the existing data. Further, it developed a scientifically supportable category of related chemicals and used structure-activity relationship information to address certain data requirements. Existing data for members of this category indicate that they are of moderate to high toxicity in the aquatic environment, and of low concern for mammalian toxicity. No testing is proposed for the chemicals that constitute the Substituted p-Phenylenediamines category for the purposes of the HPV Program.

Substituted p-Phenylenediamines category

Relying on several factors specified in EPA's guidance document on "Development of Chemical Categories in the HPV Challenge Program," in which use of chemical categories is encouraged, the following closely related chemicals constitute a chemical category:

Substituted p-Phenylenediamines

Alkylated PPD

p-Phenylenediamine, N,N-di-sec-butyl (101-96-2)
p-Phenylenediamine, N,N-bis(1,4-dimethylpentyl) (3081-14-9)

4-Aminodiphenylamine Derivatives

p-Phenylenediamine, N-Isopropyl-N'-phenyl-, (101-72-4)
p-Phenylenediamine, N-(1,3-dimethylbutyl) N'-phenyl (793-24-8)
1,4-Benzenediamine, N,N'-mixed Ph and toyl derivatives (68953-84-4)
p-Phenylenediamine, N-(1,4-dimethylpentyl) N'-phenyl (3081-01-4)
p-Phenylenediamine, N,(1-methylheptyl)-N'-phenyl, (15233-47-3)

The goal of developing a chemical category is to use interpolation and/or extrapolation to assess chemicals rather than conducting additional testing with specific consideration of animal welfare concerns to minimize the use of animals in the testing of chemicals.

Structural Similarity. A key factor supporting the classification of these chemicals as a category is their structural similarity (see Figure 1). All materials in this category are phenylenediamines with various substituent groups that are always in the *para* position of the aromatic ring. The substituent groups may be all alkyl, all aryl, or mixed alkyl/aryl.

Similarity of Physicochemical Properties. The similarity of the physicochemical properties of these materials parallels their structural similarity. All are highly-colored (dark brown, purple, reddish or black) solids or semi-viscous liquids intended for use as antidegradants in dark-colored or black finished rubber articles or functional fluids. The use of these materials requires that they be stable under high temperatures. Their low volatility is due to their low vapor pressure, semi-viscous or solid form. The existing information for these materials indicates that they have very low water solubility and high flash points.

Fate and Transport Characteristics. Members of this category have been tested and shown not to be readily biodegradable via CO2 evolution, but they are susceptible to both hydrolysis and photodegradation. Additional data collection efforts are not necessary. These materials have been shown not to partition to water or air if released into the environment due to their low water solubility and low vapor pressure; as a result additional computer-modeled environmental partitioning data is not necessary for the members of this category, for the purposes of the HPV Program.

Toxicological Similarity. Review of existing published and unpublished test data for Substituted p-Phenylenediamines shows the aquatic and mammalian toxicity among the materials within this category are similar.

> **Aquatic Toxicology**. Data on acute fish toxicity, acute invertebrate toxicity, and algae toxicity were reviewed. The Substituted p-Phenylenediamines, in general, are very toxic to aquatic organisms. Additional testing is not proposed for these materials for the purposes of the HPV Program.

Mammalian Toxicology - Acute. Data on acute mammalian toxicity were reviewed, and the findings indicate a low concern for acute toxicity for all materials. Data are available for most members of the category indicating that the category has been well tested for acute mammalian effects. Therefore, no additional acute mammalian toxicity testing is proposed for the purposes of the HPV Program.

Mammalian Toxicology - Mutagenicity. Data from bacterial reverse mutation assays, *in vitro* and *in vivo* chromosome aberration studies, as well as additional supporting *in vitro* and *in vivo* genetic toxicity studies were reviewed, and the findings indicate a low concern for mutagenicity. Data are available for several members of the category or close structural analogs, and these data can be bridged to the other members of the category. Therefore, the category has been adequately tested for mutagenicity to meet the requirements of the HPV Program; therefore, no additional mutagenicity testing is proposed.

Mammalian Toxicology – Repeated Dose Toxicity. Data from repeated-dose toxicity studies were reviewed and sufficient data are available to satisfy the repeated dose toxicity requirements of this category through bridging to members without test data, such that additional testing is not proposed for these materials for the purposes of the HPV Program.

Mammalian Toxicology - Reproductive and Developmental Toxicity. There are several adequate reproductive/developmental studies for members of the Substituted p-Phenylene diamines category. Again, existing study data and results can be bridged to other category members, such that additional testing is not proposed for the purposes of the HPV Program.

Conclusion. Based upon data reviewed for the HPV program, the physicochemical and toxicological properties of the proposed Substituted p-Phenylenediamines category members are similar and follow a regular pattern as a result of that structural similarity. Therefore, the EPA definition of a chemical category has been met. Further, the availability and results of data for the chemicals that constitute the Substituted p-Phenylenediamines category indicate that no additional testing needs to be conducted for the purposes of the HPV Program.

Introduction

A provision for the use of structure activity relationships (SAR) to reduce testing needs is included under EPA's HPV Program. Specifically, categories may be formed based on structural similarity, through analogy, or through a combination of category and analogy for use with single chemicals. The benefits of using a category approach are numerous and include accelerated release of hazard information to the public (category analysis and testing are proposed to be initiated within the first two years of the HPV Program); reduction in the number of animals used for testing; and an economic savings as a result of a reduced testing program.

The Substituted p-Phenylenediamines that form this category based on structural similarity are:

Alkylated N-PPD
p-Phenylenediamine, N,N-di-sec-butyl (101-96-2)
p-Phenylenediamine, N,N-bis(1,4-dimethylpentyl) (3081-14-9)

4-Aminodiphenylamine Derivatives
p-Phenylenediamine, N-Isopropyl-N'-phenyl-, (101-72-4)
p-Phenylenediamine, N-(1,3-dimethylbutyl) N'-phenyl (793-24-8)
1,4-Benzenediamine, N,N'-mixed Ph and toyl derivatives (68953-84-4)
p-Phenylenediamine, N-(1,4-dimethylpentyl) N'-phenyl (3081-01-4)
p-Phenylenediamine, N,(1-methylheptyl)-N'-phenyl, (15233-47-3)

The category has been arranged into two primary subcategories (Alkylated N-PPD and 4-Aminodiphenylamine Derivatives) for purposes of bridging data to the closest related material. The materials were further arranged in order of molecular weight, so that the smallest material is listed first, and the following materials have increasingly larger molecular weights. Of these, p-Phenylenediamine, N-Isopropyl-N'-phenyl-, (CAS#101-72-4) has been evaluated in the Organization for Economic Co-operation and Development (OECD) Screening Information Data Set (SIDS) program and p-Phenylenediamine, N-(1,3-dimethylbutyl) N'-phenyl (CAS#793-24-8) is currently in the OECD SIDS evaluation process. Data for these two members of the Substituted p-Phenylene diamines category are included in support of the five category members sponsored in the HPV Program.

The development of this category follows current EPA guidance[1].

Background Information: Manufacturing and Commercial Applications

Manufacturing

Substituted p-Phenylenediamines are manufactured batchwise in high-pressure autoclave reactors using a process known as catalytic reduction. In a typical reaction process, the chemical intermediate 4-Aminodiphenylamine (CAS#101-54-2) is reacted with the appropriate ketone and hydrogen gas in the presence of a precious metal catalyst on carbon to form the product, which is then purified via separation, filtration and azeotropic distillation.

Commercial Applications

In the U.S., Substituted p-Phenylenediamines are used primarily as antidegradants in the production of black or dark-colored rubber, as fuel additives and in monomer distillation processes. They are widely used in the manufacture of tires (sidewall, tread and retread, carcass, belt skim, liner, bead filler/chafer, and base tread), moldings, hoses, belts and gaskets for the automotive industry and in other industrial rubber products such as roofing material that are exposed to the elements. Others are used as fuel additives to prevent air oxidation, and a few find usage as "short-stoppers" or polymerization inhibitors in the process of monomer distillation. Substituted p-Phenylenediamines are powerful antioxidants/antiozonants that greatly extend the useful life of

[1] US EPA, Office of Pollution Prevention and Toxics. Development of Chemical Categories, Chemical Right-to-Know Initiative. http://www.epa.gov/opptintr/chemrtk/categuid.htm

rubber articles and functional fluids by delaying the oxidative aging process. These highly-colored, or "staining" antidegradants also help prevent surface cracking due to flex fatigue in dynamic applications. Typical usage level for the Substituted p-Phenylenediamines in these industrial applications ranges from 0.5 – 3%.

FDA Status – The Substituted p-Phenylenediamines are not widely used in food contact applications due to their capability to stain and discolor. However, two chemicals in this category have some limited food-contact applications:

175.105	Components of Adhesives	68953-84-4
177.2600	Rubber Articles	68953-84-4 and 101-72-4

Shipping/Distribution

Substituted p-Phenylenediamines are shipped extensively throughout the world from manufacturing plants located in North and South America, Eastern and Western Europe, China and Japan. These materials are typically shipped by tank car, tank truck, and barge.

Worker/Consumer Exposure

The rubber and plastics additives industry has a long safety record and sophisticated industrial users handle materials. Exposure of workers handling PPD category chemicals is likely to be the highest in the area of material packaging rather than manufacturing. These materials are made as pastilles (pellets), powders, flakes, solids and liquids. Thus, during the transfer operation from the manufacturing process to packaging there is a potential for inhalation exposure (nuisance dust is the primary route of worker exposure) and dermal contact to liquid forms. There should be little, if any, consumer exposure to substituted p-phenylenediamines since these materials will be part of finished articles, and as such unavailable for exposure or release under typical conditions of use.

Development of the Substituted p-Phenylenediamines Category

EPA has described a stepwise process for developing categories. These steps include:

- Grouping a series of like chemicals, including the definition of criteria for the group.
- Gathering data on physicochemical properties, environmental fate and effects, and health effects for each member of the category.
- Evaluating the data for adequacy.
- Constructing a matrix of available and unavailable data.
- Determining whether there is a correlation among category members and data gathered.

Definition of the Substituted p-Phenylenediamines Category

As defined by EPA under the HPV Program, a chemical category is "a group of chemicals whose physicochemical and toxicological properties are likely to be similar or follow a regular pattern as a result of structural similarity." The similarities should be based on a common functional group, common precursors or

breakdown products (resulting in structurally similar chemicals) and an incremental and constant change across the category. The goal of developing a chemical category is to use interpolation and/or extrapolation to assess chemicals rather than conducting additional testing with specific consideration of animal welfare concerns to minimize the use of animals in the testing of chemicals.

The materials within the Substituted p-Phenylenediamines category, for the purposes of the HPV Program, are defined as phenylenediamines with alkyl, aryl or mixed alkyl-aryl substitutions, as illustrated in Figure 1.

The category referred to as Substituted p-Phenylenediamines is further categorized into two secondary subcategories; Alkylated N-PPD and 4-Aminodiphenylamine derivatives. The Alkylated N-PPD materials are structurally similar in that both N groups are alkylated, while the 4-Aminodiphenylamine Derivatives materials all contain aryl and alkyl substituted groups. Chemical structures for these materials are provided in Figure 2. The very low water solubility, low vapor pressure, slow biodegradation, low bioaccumulation potential, rapid hydrolysis and photodegradation are similar for the Substituted p-Phenylene Diamines (see Tables 1 and 3). These highly-colored, staining compounds also exhibit high flash points (see Table 1).

Matrix of SIDS Endpoints

In order to construct a matrix of SIDS endpoints for the members of the Substituted p-Phenylenediamines category, the data on physicochemical properties, environmental fate and effects, and health effects for each member of the category must be collected and evaluated for adequacy. The results of these activities are presented in the tables and text below, providing a matrix of available data for the Substituted p-Phenylenediamines materials.

Correlation within the Substituted p-Phenylenediamines Category

The matrix data patterns for physicochemical properties; environmental fate, ecotoxicity; and health effects have been evaluated for the members of the Substituted p-Phenylenediamines category. A description of the results of this evaluation follows.

Correlation of Physicochemical Properties

The physicochemical properties of the members of the Substituted p-Phenylenediamines category are presented in Table 2. These materials may exist as viscous liquids or solids at room temperature, such that melting point or boiling point data may be relevant for varying members of the category. The similarities in the other physicochemical properties of these materials, which are described below, are explained by similarities in their chemical structure, and provide justification of this group of chemicals as a category within the HPV Challenge Program.

The members of this category have a wide range of melting points and boiling points (varying based on the physical state as a liquid or solid). Six members of this category have very low vapor pressures, as indicated in Table 2. Data for six members of this category clearly indicate a lack of water solubility or negligible water solubility. Partition coefficient data are primarily in the range of 3 to 5.

Bridging to other members of the category or use of EPIWIN modeling will be used to fill physicochemical properties data requirements for the purposes of the HPV Program, as illustrated below, and in Table 1.

Alkylated N-PPD: Sufficient data exist for the Alkylated N-PPD materials for the purposes of the HPV Program.

4-Aminodiphenylamine Derivatives: Physicochemical properties data (boiling point and vapor pressure) for p-Phenylenediamine, N-(1,3-dimethylbutyl) N'-phenyl (793-24-8) are provided by EPIWIN modeling. Vapor pressure, boiling point and water solubility data will be bridged from p-Phenylenediamine, N-(1,4-dimethylpentyl) N'-phenyl (3081-01-4) to 1,4-Benzenediamine, N,N'-mixed Ph and toyl derivatives (68953-84-4). Partition coefficient data for p-Phenylenediamine, N-(1,4-dimethylpentyl) N'-phenyl (3081-01-4) will be bridged to p-Phenylenediamine, N,(1-methylheptyl)-N'-phenyl, (15233-47-3). EPIWIN was used to provide melting point and vapor pressure data for p-Phenylenediamine, N,(1-methylheptyl)-N'-phenyl, (15233-47-3).

Correlation of Environmental Fate

The members of this category are generally found to be not readily biodegradable by CO_2 generation, but photodegradation is rapid, as is hydrolysis. Analytical studies of hydrolysis products indicate that the molecule cleaves at the aromatic carbon-nitrogen bond.

The HPV Challenge Program requires that hydrolysis, photodegradation, biodegradation and environmental transport information be presented for each material or bridged to each member of a category. Adequate biodegradation data exist for several of the materials in this category for the purposes of the HPV Program; bridging will be used to fill the remaining biodegradation data requirements as illustrated below. The results presented indicate that these materials are poorly biodegradable, with the exception of p-Phenylenediamine, N-Isopropyl-N'-phenyl-, (101-72-4) and p-Phenylenediamine, N-(1,3-diemthylbutyl) N'-phenyl-, (793-24-8). Hydrolysis data exists for several members of this group, and gas chromatography identification and quantification of hydrolysis products suggests a common breakdown mechanism exists. Photodegradation studies presented for several members of this category are adequate for the purposes of the HPV Program; bridging will be used to fill the remaining photodegradation data requirements as illustrated below. Finally, fugacity modeling has been conducted on six of the seven members of this category, with consistent results showing partitioning to soil and/or sediment. This finding is consistent with the lack of water solubility and low vapor pressure of these materials. Bridging to other members of the category will fill environmental transport data requirements, as illustrated below.

Alkylated N-PPD: The hydrolysis data for p-Phenylenediamine, N,N-bis(1,4-dimethylpentyl) (3081-14-9) will be bridged to p-Phenylenediamine, N,N-di-sec-butyl (101-96-2). Biodegradation and photodegradation data for p-Phenylenediamine, N,N-di-sec-butyl (101-96-2) was modeled using EPIWIN.

4-Aminodiphenylamine Derivatives: Photodegradation, hydrolysis, and environmental transport data will be bridged from p-Phenylenediamine, N-(1,3-dimethylbutyl) N'-phenyl (793-24-8) to 1,4-Benzenediamine, N,N'-mixed Ph and toyl derivatives (68953-84-4). Photodegradation data was modeled using EPIWIN for p-

Phenylenediamine, N-Isopropyl-N'-phenyl-, (101-72-4), p-Phenylenediamine, N-(1,3-dimethylbutyl) N'-phenyl (793-24-8), p-Phenylenediamine, N-(1,4-dimethylpentyl) N'-phenyl (3081-01-4 and p-Phenylenediamine, N,(1-methylheptyl)-N'-phenyl, (15233-47-3).

Biodegradation data for p-Phenylenediamine, N,(1-methylheptyl)-N'-phenyl, (15233-47-3) was modeled using EPIWIN.

Correlation of Ecotoxicity

The HPV Challenge Program requires that an acute aquatic ecotoxicity test in fish, invertebrates, and algae be performed or bridged to each member of a category. Existing data (Table 4) indicate that six members of the Substituted p-Phenylenediamines category have low water solubility. The low water solubility suggests that the acute aquatic toxicity of these materials should be low due to limited bioavailability to aquatic organisms. However, the Substituted p-Phenylenediamines, in general, are very toxic to aquatic organisms. Additional testing is not necessary for these materials for the purposes of the HPV Program.

Alkylated N-PPD: Results of acute aquatic toxicity studies show p-Phenylenediamine, N, N-bis(1,4-dimethylpentyl) (3081-14-9) is harmful to algae, and very toxic to fish and Daphnia. P-Phenylenediamine, N, N-di-sec-butyl (101-96-2) was very toxic to fish and toxic to Daphnia in acute aquatic studies. The algal growth inhibition data for p-Phenylenediamine, N, N-bis(1,4-dimethylpentyl) (3081-14-9) will be bridged to p-Phenylenediamine, N, N-di-sec-butyl (101-96-2).

4-Aminodiphenylamine Derivatives: Aquatic toxicity data exist for four of the five members of this subcategory. The results of aquatic toxicity testing of these materials indicate they are toxic to very toxic to fish, Daphnia, and algae in acute studies.

The acute aquatic toxicity data for p-Phenylenediamine, N-(1,4-dimethylpentyl) N'-phenyl (3081-01-4) will be bridged p-Phenylenediamine, N,(1-methylheptyl)-N'-phenyl, (15233-47-3).

Correlation of Health Effects

Acute Mammalian Toxicity

Acute oral and dermal toxicity data for the Substituted p-Phenylenediamines category are summarized in Table 5. The two materials in the Alkylated N-PPD subcategory of the Substituted p-Phenylene Diamines show a moderate order of acute oral toxicity. The second subcategory, the 4-Aminodiphenylamine derivatives, all have a very low order of toxicity, with LD50 values greater than the limit test of 2000 mg/kg with the exception of p-Phenylenediamine, N-Isopropyl-N'-phenyl-, (101-72-4), with an oral LD50 of 900 mg/kg. Acute dermal toxicity data for all members of the Substituted p-Phenylenediamines category demonstrate a very low order of toxicity with the dermal LD50 values greater than the limit test of 2000 mg/kg.

Adequate acute toxicity studies have been conducted for the Substituted p-Phenylenediamines category. These studies involved at least two routes of exposure (oral and dermal); and evaluated the toxicity of all the members of the category. The data demonstrate a moderate to very low order of acute toxicity. The trend in acute oral

toxicity follows the molecular weight of the materials. That is, there is a general trend toward decreasing acute oral toxicity with increasing molecular weight. The similarity in the order of toxicity for these materials is consistent with their similar chemical structure and physicochemical properties and supports the scientific justification of these materials as a category within the HPV Challenge Program.

The HPV Challenge Program requires that either an acute test be performed or bridged to each member of a category. Adequate acute oral and dermal toxicity tests exist for the Substituted N-Phenylenediamines for the purposes of the HPV Program.

Mutagenicity

A summary of the mutagenicity information for the Substituted p-Phenylenediamines category is presented in Table 6. The weight of evidence for the members of this category indicates these materials are not mutagenic.

Adequate bacterial mutagenicity tests have been conducted for all seven of the Substituted N-Phenylene diamines category to satisfy HPV Challenge requirements. Similarly, adequate *in vitro* chromosome aberration tests or *in vivo* micronucleus tests have been conducted for five of the seven materials in the Substituted N-Phenylenediamines category; additional *in vitro* or *in vivo* mammalian mutagenicity studies are available as supporting information; bridging will be used to fill the remaining data requirement.

Bacterial Gene Mutation Assay

With one exception, mutagenicity was not exhibited by any of the materials in the Substituted p-Phenylenediamines category in the bacterial mutagenicity tests with or without metabolic activation. The single exception was a positive response with 1,4-Benzenediamine, N,N'-mixed Ph and toyl derivatives (68953-84-4).

In vivo Chromosomal Aberration Assays (Mammalian Micronucleus Test)

Three of the seven Substituted p-Phenylenediamine materials have been adequately tested in an *in vivo* chromosomal aberration assay for HPV Challenge requirements. The results were negative for clastogenicity.

In vitro Chromosomal Aberration Assay

Six of the seven Substituted p-Phenylenediamine materials have been adequately tested in an *in vitro* chromosomal aberration assay using Chinese hamster ovary cells to satisfy Program requirements. The results of these studies, performed with and without metabolic activation of the test material, were negative for clastogenicity with the exception of p-Phenylenediamine, N-(1,4-dimethylpentyl) N'-phenyl (3081-01-4).

The Substituted p-Phenylenediamines category has been adequately tested for mutagenicity in tests for gene mutations and chromosomal aberrations for purposes of meeting HPV Challenge requirements. The assays included point mutations in bacterial cells, *in vitro* chromosomal aberrations in mammalian cells, and *in vivo* chromosomal aberrations. The data consistently demonstrate no evidence of genotoxicity for this category of materials. 1,4-Benzenediamine, N,N'-mixed Ph and toyl derivatives (68953-84-4) was positive in the bacterial mutagenicity test, but was negative in both in vitro and in vivo mammalian mutagenicity studies. p-Phenylenediamine, N-(1,4-dimethylpentyl) N'-phenyl (3081-01-4) was positive for clastogenicity in the *in vitro* chromosome aberration test, but was negative in the *in vivo* mouse micronucleus test. This suggests that all

members of the category lack genotoxicity due to their similarity in chemical structures and physicochemical properties. The similarity of results for genotoxicity supports treatment of these materials as a chemical category within the HPV Challenge Program.

The HPV Challenge Program requires that a gene mutation and a chromosomal aberration test be performed or bridged to each member of a category. Bridging will be used to fill the remaining data requirements.

Alkylated N-PPD: Sufficient data exist for the Alkylated N-PPD materials for the purposes of the HPV Program.

4-Aminodiphenylamine Derivatives: Data from *in vivo* mutagenicity testing with p-Phenylenediamine, N-(1,3-dimethylbutyl) N'-phenyl (793-24-8) will be bridged to p-Phenylenediamine, N-Isopropyl-N'-phenyl-, (101-72-4). Mutagenicity test data from p-Phenylenediamine, N-(1,4-dimethylpentyl) N'-phenyl (3081-01-4) will be bridged to p-Phenylenediamine, N,(1-methylheptyl)-N'-phenyl, (15233-47-3).

By bridging these data, the category has been evaluated adequately for genotoxicity for the purposes of the HPV Program, and no additional testing is proposed**.**

Repeat Dose Toxicity

A summary of the repeat dose toxicity data for the Substituted p-Phenylene Diamines category is presented in Table 7.

Alkylated N-PPD: Adequate repeat dose studies are available for both the Alkylated N-PPD materials for the purposes of the HPV Program. P-Phenylenediamine, N, N-bis (1,4-dimethylpentyl) (3081-14-9) was given in the diet to rats at levels of 0, 100, 300, 500, 1000, or 2000 ppm (5/sex/group) for four weeks. Males at 300 ppm and above and females at 1000 ppm and above showed a reduced body weight gain. Alterations in hematology and clinical chemistry parameters were noted at the two highest dose levels. The No Observed Effect Level (NOEL) for males and females was 100 and 300 ppm, respectively. 100 male and female rats (10/sex/dose level) were dosed with p-Phenylenediamine, N, N-di-sec-butyl (101-96-2) in corn oil vehicle at 0, 10, 25, 50, or 100 mg/kg for a period of 28 days. Because the results of this study demonstrated hepatic effects in both sexes and at all treatment levels, a NOEL could not be established.

4-Aminodiphenylamine Derivatives: Adequate repeat dose studies are available for four of the five 4-Aminodiphenylamine Derivatives materials for the purposes of the HPV Program.

Subchronic studies have been conducted with p-Phenylenediamine, N-Isopropyl-N'-phenyl-, (101-72-4). When administered to rats in the diet at levels of 0, 500, 1000, 1750 and 2500 ppm for four weeks, decreases in body weight gains, hematological effects, elevations in total serum protein and increased lever and spleen weight were noted at 1000 ppm and above. The NOEL was identified as 500 ppm. In a 90-day study, p-Phenylenediamine, N-Isopropyl-N'-phenyl-, (101-72-4) was administered to rats in the diet at levels of 0, 180, 360 or 720 ppm. Lower body weight gains were observed in high-dose males; increased absolute and relative liver weights were noted in mid- and high-dose males and all treated females. Increased spleen and kidney weights were observed in high-dose females, and mild anemia was noted in mid- and high-dose animals. There

were no treatment related gross or histopathological changes noted in any group. A NOEL for organ weight changes was not established for females, while a NOEL for males was 180 ppm.

Dietary administration of p-Phenylenediamine, N-(1,4-dimethylpentyl) N'-phenyl (3081-01-4) at 0, 500, 750, 1500 or 3000 ppm to rats for one month resulted in reduced food consumption and decreased weight gain at the three highest doses in both sexes. No gross pathology or other signs of toxicity were noted. The NOEL was identified as 500 ppm in the diet.

Dietary administration of 1,4-Benzenediamine, -mixed Ph and toyl derivatives (68953-84-4) at concentrations of 0, 120, 470 and 1900 ppm (0, 7.5, 30 and 120 mg/kg/day) to rats for 28 days resulted in body weight decreases in high dose female rats and decreased food consumption in high-dose males and mid- and high-dose females. Hematological changes (high dose), liver and kidney weight increases (high-dose male and female, mid-dose females). The No Observed Adverse Effects Level (NOAEL) for this study was established at 7.5 mg/kg. A 21-day gavage range-finding study was also conducted with rats with this material at doses of 0, 0.1, 0.3, 1 and 3 g/kg/day. Lethality was observed at 1 and 3 g/kg/day. Body weight gain loss, liver weight increase and hepatocellular labeling index increase were noted at 0.3 and/or 0.1 g/kg/day.

Santoflex 13 (p-Phenylenediamine, N-(1,3-dimethylbutyl) N'-phenyl (793-24-8)) was administered in feed to groups of 6 week old male and female rats at 0, 250, 1000 or 2500 ppm. Analyses via GC verified feeding levels of 0, 230, 950 and 2300 ppm. All animals survived the length of the study. Signs of toxicity during the study were limited to reduced feed consumption/body weight gain in the high-dose males and females and mid-level males. Anemia, lymphocytopenia and thrombocytosis were present in males and females, primarily at the two highest dose levels. Increases in total bilirubin in males, and total protein, albumin, globulin, calcium and/or cholesterol in both sexes were noted in high and some mid-dose level animals. Increased liver weights were observed at the two highest dose levels. There were no gross or microscopic lesions attributed to consumption of the test material. Females at low dose levels exhibited mild anemia at the interim sampling period, but all recovered by the end of the study. Therefore, the NOEL was considered to be 250 ppm.

Repeat dose data from p-Phenylenediamine, N-(1,4-dimethylpentyl) N'-phenyl (3081-01-4) will be bridged to p-Phenylenediamine, N,(1-methylheptyl)-N'-phenyl, (15233-47-3).

By bridging these data, the category has been evaluated adequately for genotoxicity for the purposes of the HPV Program, and therefore, no additional testing is proposed**.**

Reproductive and Developmental Toxicity A summary of the reproductive and developmental toxicity data for the Substituted p-Phenylenediamines category is presented in Table 7.

Alkylated N-PPD: Adequate reproductive toxicity studies are available for the purposes of the HPV Program for one of the two Alkylated N-PPD materials. P-Phenylenediamine, N, N-bis (1,4-dimethylpentyl) (3081-14-9) was not embryotoxic, fetotoxic or teratogenic when administered by gavage at doses of 0, 25, 75 or 150 mg/kg/day to pregnant rats on gestation days 6-15. Administration of CAS No. 3081-14-9 at dietary concentrations of 0, 30, 100 or 300 ppm to male and female rats for three successive generations produced no adverse effects on mating or fertility indices. Reduced survival of offspring was observed in mid- and high-dose

groups; however, evidence of parental toxicity was also present as indicated by reduced body weight gains of mid- and high-dose groups. The NOEL was 30 ppm. The developmental and reproductive studies with p-Phenylenediamine, N, N-bis (1,4-dimethylpentyl) (3081-14-9 will be bridged to p-Phenylenediamine, N, N-di-sec-butyl (101-96-2).

4-Aminodiphenylamine Derivatives: Adequate reproductive and developmental toxicity studies are available for three of the five 4-Aminodiphenylamine Derivatives materials for the purposes of the HPV Program.

p-Phenylenediamine, N-Isopropyl-N'-phenyl-, (101-72-4) was administered to rats by gavage at dose levels of 0, 12.5, 62.5 or 125 mg/kg/day for gestation days 6-15. The NOEL for maternal toxicity was determined to be 62.5 mg/kg. There were significant skeletal effects at 125 mg/kg and the NOEL for teratogenicity was established at 62.5 mg/kg.

1,4-Benzenediamine, N, N'-mixed Ph and toyl derivatives (68953-84-4) was administered in feed at 0, 120, 400 or 1500 ppm to rats in a two-generation reproductive toxicity study. Dystocia (potentially leading to prolonged gestation and increased perinatal deaths, decreased live births and increased pup weights), and polycystic lesions were observed at all dose levels; a NOAEL was not established in this study. A developmental study was also conducted with 1,4-Benzenediamine, N, N'-mixed Ph and toyl derivatives (68953-84-4) in rats. The test article was administered by gavage at dose levels of 0, 20, 70 and 200 mg/kg/day for gestation days 6-15. The test article produced minimal effects (body weight) to maternal rats at 200 mg/kg during pregnancy; the NOAEL for maternal toxicity was established at 70 mg/kg/day. There were no birth defects observed in fetal animals and the NOAEL for teratogenicity/developmental effects was established at 200 mg/kg/day.

A reproductive oral gavage study was conducted in rats with p-Phenylenediamine, N-(1,3-dimethylbutyl) N'-phenyl (793-24-8); no reproductive effects were observed at the highest concentration tested (1000 ppm). In a rat gavage developmental study, the test article was administered by gavage at dose levels of 0, 50, 100 and 250 mg/kg/day for gestation days 6-15. A NOAEL (teratogenicity /developmental effects) greater than 250 mg/kg/day was determined. The NOEL for maternal toxicity was established at 50 mg/kg/day.

Data from these three studies materials will be bridged to p-Phenylenediamine, N- (1,4-dimethylpentyl) N'-phenyl (3081-01-4) and p-Phenylenediamine, N, (1-methylheptyl)-N'-phenyl, (15233-47-3).

Test Plan

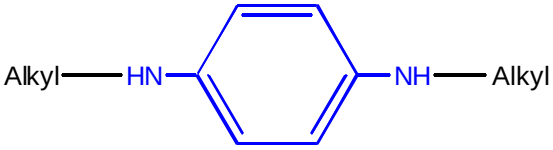
Table 8 provides the category test plan for the Substituted p-Phenylenediamines. All HPV endpoint requirements are fulfilled by existing adequate data, calculated data, or by bridging data based on SAR and the category approach. The chemicals that constitute the Substituted p-Phenylenediamines category require no additional testing for the purposes of the HPV Program.

FIGURES

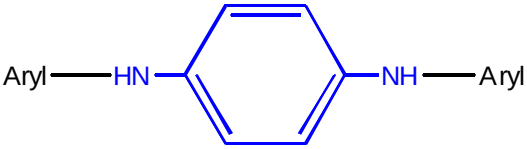
Figure 1. Structural Definition

Phenylenediamine with various aryl or alkyl substitutions in the para position:

Alkyl-N-Phenyl-N-Alkyl (all Alkyl)
Aryl-N-Phenyl-N-Aryl (All Aryl)
Alkyl-N-Phenyl-N-Aryl (Mixed Alkyl-Aryl)



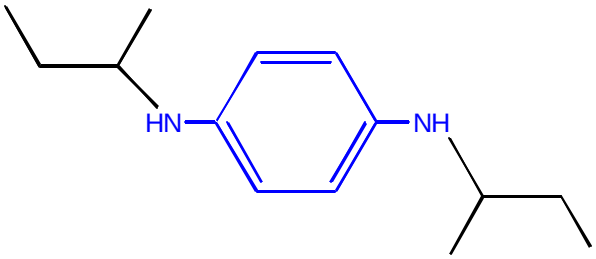
Alkyl-Alkyl Substitutions



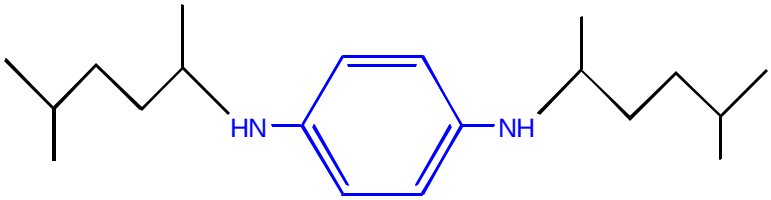
Aryl-Aryl Substitutions

Mixed Alkyl-Aryl Substitutions

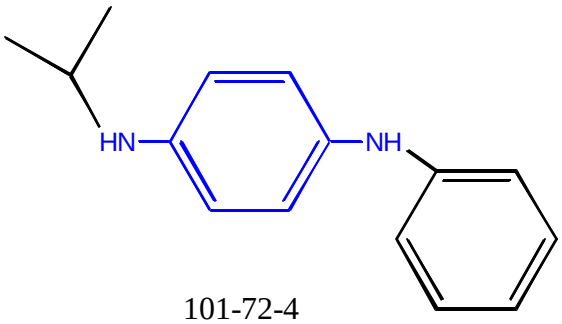
FIGURE 2. Chemical Structures



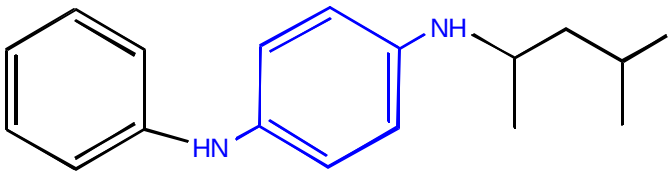
101-96-2
Alkyl-Alkyl



3081-14-9
Alkyl-Alkyl

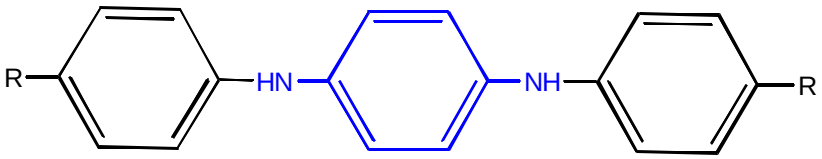


101-72-4
Alkyl-Aryl

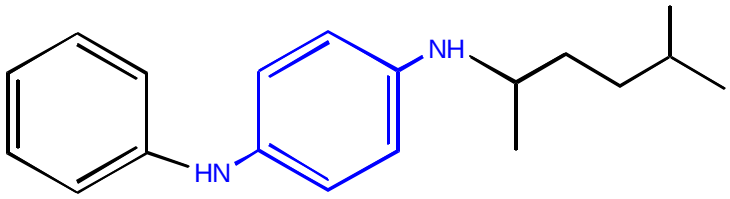


793-24-8
Alkyl-Aryl

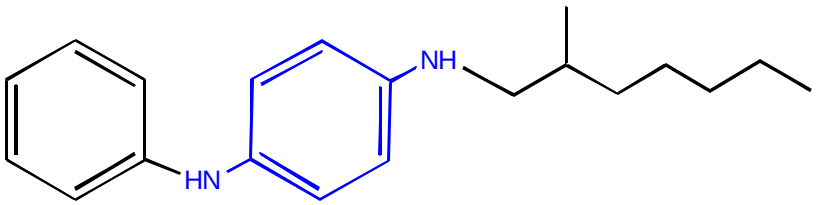
R = H or CH3



68953-84-4
Aryl-Aryl (Mixed)



3081-01-4
Alkyl-Aryl



15233-47-3
Alkyl-Aryl

TABLES

Table 1. Justification of the Substituted p-Phenylenediamines Category using Flash Point, Vapor Pressure, Water Solubility and Biodegradation

Name (CAS No.)/ Molecular weight	Flash Point (^{o}F)	Vapor Pressure (mm Hg @ 20^{o}C)	Water Solubility	Bio-degradability
Alkylated N-PPD				
p-Phenylenediamine, N,N-di-sec-butyl (101-96-2)/ 220.4	290	85.3 @ 33C	Insoluble	Not readily biodegradable
p-Phenylenediamine, N,N-bis(1,4-dimethylpentyl) (3081-14-9)/ 304	182	1.1 @ 25C	Very Slight	Not readily biodegradable
4-Aminodiphenylamine derivatives				
p-Phenylenediamine, N-Isopropyl-N'-phenyl-, (101-72-4)/ 226.4	>200 C	3.4E-5 @ 90C	Insoluble	Readily biodegradable
p-Phenylenediamine, N-(1,3-dimethylbutyl) N'-phenyl (793-24-8)/ 268.5	400	4.93E-6 @ 25C (EPIWIN)	Insoluble	Readily biodegradable
1,4-Benzenediamine, N,N'-mixed Ph and toyl derivatives (68953-84-4)/ 274	450	Not determined	Not determined	Not readily biodegradable
p-Phenylenediamine, N-(1,4-dimethylpentyl) N'-phenyl (3081-01-4)/ 282	420	1.25E-10 @25C	Insoluble	Not readily biodegradable
p-Phenylenediamine, N,(1-methylheptyl)-N'-phenyl, (15233-47-3)/ 296	Not determined	4.99E-7 @ 25C (EPIWIN)	Insoluble	Not readily biodegradable

Table 2. Matrix of Available and Adequate Data on Substituted p-Phenylenediamines Category Members Physicochemical Properties

Name (CAS No.)	Melting Point (^{o}C)	Vapor Pressure (mm Hg @ 20^{o}C)	Boiling Point (^{o}C)	Partition Coefficient	Water Solubility
Alkylated N-PPD					
p-Phenylenediamine, N,N-di-sec-butyl (101-96-2)	18	85.3 @ 38 C	98 @ 26.6hPa	3.50	<1 mg/ml @ 20C
p-Phenylenediamine, N,N-bis(1,4-dimethylpentyl) (3081-14-9)	-36	<1.1E-6 @ 25C	183.5 @ 1mm Hg	5.34	21 ppm @ pH5; 0.8 ppm @ pH 9
4-Aminodiphenylamine derivatives					
p-Phenylenediamine, N-Isopropyl-N'-phenyl-, (101-72-4)	75-80	3.4E-3 @90C	161	3.28	15 ppm @25C
p-Phenylenediamine, N-(1,3-dimethylbutyl) N'-phenyl (793-24-8)	45	4.93E-6 @25C (EPIWIN)	369.67 (EPIWIN)	4.7	1 ppm @ 23C
1,4-Benzenediamine, N,N'-mixed Ph and toyl derivatives (68953-84-4)	90-105	Not determined	Not determined	3.4-4.3	Not determined
p-Phenylenediamine, N-(1,4-dimethylpentyl) N'-phenyl (3081-01-4)	32	1.25E-10 @ 25C	231 @3.5 mmHg	5.17	0.67g/l @ 25C
p-Phenylenediamine, N,(1-methylheptyl)-N'-phenyl, (15233-47-3)	145.77 (EPIWIN)	4.99E-7 @ 25C (EPIWIN)	431	Not determined	Insoluble

Table 3. Matrix of Available and Adequate Data on Substituted p-Phenylenediamines Category Members Environmental Fate

Name (CAS No.)	Hydrolysis	Photo-degradation (t1/2 in hours)	Bio-degradation	Environmental Transport
Alkylated N-PPD				
p-Phenylenediamine, N, N-di-sec-butyl (101-96-2)	Not determined	1.095 (EPIWIN)	Not readily biodegradable (EPIWIN)	Primarily to soil
p-Phenylenediamine, N, N-bis(1,4-dimethylpentyl) (3081-14-9)	97%@pH7 after 24 hr	2	50% after 35 days	Primarily to sediment
4-Aminodiphenylamine derivatives				
p-Phenylenediamine, N-Isopropyl-N'-phenyl-, (101-72-4)	99%@pH7 after 24 hr	0.588 (EPIWIN)	98% after 22 hours	Primarily to soil
p-Phenylenediamine, N-(1,3-dimethylbutyl) N'-phenyl (793-24-8)	93%@pH7 after 24 hr	0.567 (EPIWIN)	50 % after 2.9 hours	Primarily to soil
1,4-Benzenediamine, N, N'-mixed Ph and toyl derivatives (68953-84-4)	Not determined	Not determined	0.64% after 28 days	Not determined
p-Phenylenediamine, N-(1,4-dimethylpentyl) N'-phenyl (3081-01-4)	96%@pH7 after 24 hr	0.563 (EPIWIN)	0% @ 35days	Primarily to soil
p-Phenylenediamine, N,(1methylheptyl)-N'-phenyl, (15233-47-3)	Not determined	0.56 (EPIWIN)	Not readily biodegradable (EPIWIN)	Primarily to soil and sediment

Table 4. Matrix of Available and Adequate Data on Substituted p-Phenylenediamines Category Members Ecotoxicity

Name (CAS No.)	Acute Fish 96-hour LC50 (mg/l)	Acute Invertebrate 48-hour EC50 (mg/l)	Algal growth inhibition 96-hour EC50 (mg/l)
Alkylated N-PPD			
p-Phenylenediamine, N,N-di-sec-butyl (101-96-2)	0.13	1.4	Not determined
p-Phenylenediamine, N,N-bis(1,4-dimethylpentyl) (3081-14-9)	0.28	0.37	52
4-Aminodiphenylamine derivatives			
p-Phenylenediamine, N-Isopropyl-N'-phenyl-, (101-72-4)	0.34	1.1	0.5 (cell growth)
p-Phenylenediamine, N-(1,3-dimethylbutyl) N'-phenyl (793-24-8)	0.14-0.4	0.82	0.6
1,4-Benzenediamine, N,N'-mixed Ph and toyl derivatives (68953-84-4)	0.48	1.8	(72-hour EC50) 0.018 (biomass); >0.079 (growth rate)
p-Phenylenediamine, N-(1,4-dimethylpentyl) N'-phenyl (3081-01-4)	0.3-1.1	0.2	0.7
p-Phenylenediamine, N,(1methylheptyl)-N'-phenyl, (15233-47-3)	Not determined	Not determined	Not determined

Table 5. Matrix of Available and Adequate Data on Substituted p-Phenylenediamines Category Members
Acute Toxicity

Name (CAS No.)	Acute Oral (mg/kg)	Acute Dermal (mg/kg)
Alkylated N-PPD		
p-Phenylenediamine, N,N-di-sec-butyl (101-96-2)	271	2806
p-Phenylenediamine, N,N-bis(1,4-dimethylpentyl) (3081-14-9)	730	>3160
4-Aminodiphenylamine derivatives		
p-Phenylenediamine, N-Isopropyl-N'-phenyl-, (101-72-4)	900	>7940
p-Phenylenediamine, N-(1,3-dimethylbutyl) N'-phenyl (793-24-8)	>5000	>7940
1,4-Benzenediamine, N,N'-mixed Ph and toyl derivatives (68953-84-4)	>2000	>2000
p-Phenylenediamine, N-(1,4-dimethylpentyl) N'-phenyl (3081-01-4)	>2000	>5010
p-Phenylenediamine, N,(1-methylheptyl)-N'-phenyl, (15233-47-3)	4300	>2000

Table 6. Matrix of Available and Adequate Data on Substituted p-Phenylenediamines Category Members Genotoxicity

Name (CAS No.)	Genotoxicity (*in vitro* - bacterial)	Genotoxicity (*in vitro* - mammalian)	Genotoxicity (*in vivo*)
Alkylated N-PPD			
p-Phenylenediamine, N,N-di-sec-butyl (101-96-2)	Negative	Negative	Not determined
p-Phenylenediamine, N,N-bis(1,4-dimethylpentyl) (3081-14-9)	Negative	Negative	Not determined
4-Aminodiphenylamine derivatives			
p-Phenylenediamine, N-Isopropyl-N'-phenyl-, (101-72-4)	Negative	Negative	Not determined
p-Phenylenediamine, N-(1,3-dimethylbutyl) N'-phenyl (793-24-8)	Negative	Negative	Negative
1,4-Benzenediamine, N,N'-mixed Ph and toyl derivatives (68953-84-4)	Positive	Negative	Negative
p-Phenylenediamine, N-(1,4-dimethylpentyl) N'-phenyl (3081-01-4)	Negative	Weak Positive; Supporting data Negative	Negative
p-Phenylenediamine, N,(1methylheptyl)-N'-phenyl, (15233-47-3)	Negative	Not determined	Not determined

Table 7. Matrix of Available and Adequate Data on Substituted p-Phenylenediamines Category Members Health Effects

Name (CAS No.)	Repeat Dose	Reproductive	Developmental
Alkylated N-PPD			
p-Phenylenediamine, N,N-di-sec-butyl (101-96-2)	28-Day oral gavage with rats. NOEL< 10 mg/kg/day	Not determined	Not determined
p-Phenylenediamine, N,N-bis(1,4-dimethylpentyl) (3081-14-9)	30 day feeding study with rats. NOEL (males) 100 pm; (females) 300 ppm	Three generation rat oral feeding study; NOEL(parental, F1 and F2 offspring) = 30 ppm	Rat gavage: NOEL (teratogenicity) = >150 mg/kg/day; (maternal) = 25 mg/kg/day
4-Aminodiphenylamine derivatives			
p-Phenylenediamine, N-Isopropyl-N'-phenyl-, (101-72-4)	90-day feeding study with rats. NOEL (males) 180 ppm; NOEL not established (females)	Not determined	Rat gavage: NOEL (teratogenicity) = 62.5, (maternal) 62.5 mg/kg/day
p-Phenylenediamine, N-(1,3-dimethylbutyl) N'-phenyl (793-24-8)	90-day oral rat-NOAEL = 250 ppm in feed	Rat gavage – NOEL (parental) >1000 ppm; (F1 offspring) >1000 ppm	Rat gavage: NOAEL (teratogenicity /developmental effects) = 250 mg/kg/day; NOEL (maternal) = 50 mg/kg/day
1,4-Benzenediamine, N,N'-mixed Ph and toyl derivatives (68953-84-4)	28-day rat oral NOAEL = 7.5 mg/kg	Two generation rat oral feeding study – NOEL not identified	Rat gavage: NOAEL (teratogenicity /developmental effects) $\leq$ 200 mg/kg/day, NOAEL (maternal toxicity 70 mg/kg/day)
p-Phenylenediamine, N-(1,4-dimethylpentyl) N'-phenyl (3081-01-4)	1 month feeding study with rats – NOEL = 500 ppm in diet	Not determined	Not determined
p-Phenylenediamine, N,(1methylheptyl)-N'-phenyl, (15233-47-3)	Not determined	Not determined	Not determined

.

Table 8

Substituted p-Phenylenediamines Category Test Plan

CAS Nos. 101-96-2, 3081-14-9, 101-72-4, 793-24-8, 3081-01-4, 15233-47-3, and 68953-84-4
Rubber and Plastic Additives Panel American Chemistry Council
December 2001

	Physical-Chemical				
CHEMICAL	**Melting Point**	**Boiling Point**	**Vapor Pressure**	**Partition Coefficient**	**Water Solubility**
Alkylated N-PPD					
p-Phenylenediamine, N,N-di-sec-butyl (101-96-2)	A	A	A	A	A
p-Phenylenediamine, N,N-bis(1,4-dimethylpentyl) (3081-14-9)	A	A	A	A	A
4-Aminodiphenylamine derivatives					
p-Phenylenediamine, N-Isopropyl-N'-phenyl-, (101-72-4)	A	A	A	A	A
p-Phenylenediamine, N-(1,3-dimethylbutyl) N'-phenyl (793-24-8)	A	Calc	Calc	A	A
1,4-Benzenediamine, N,N'-mixed Ph and toyl derivatives (68953-84-4)	A	R	R	A	R
p-Phenylenediamine, N-(1,4-dimethylpentyl) N'-phenyl (3081-01-4)	A	A	A	A	A
p-Phenylenediamine, N,(1methylheptyl)-N'-phenyl, (15233-47-3)	R	A	Calc	R	A

Legend	
Symbol	**Description**
R	Endpoint requirement fulfilled using category approach, SAR
Test	Endpoint requirements to be fulfilled with testing
Calc	Endpoint requirement fulfilled based on calculated data
A	Endpoint requirement fulfilled with adequate existing data
NR	Not required per the OECD SIDS guidance
NA	Not applicable due to physical/chemical properties

Table 8 (continued)

CHEMICAL	Environmental Fate			
	Photo-degradation	Hydrolysis	Environmental Transport	Biodegradation
Alkylated N-PPD				
p-Phenylenediamine, N,N-di-sec-butyl (101-96-2)	Calc	R	Calc	Calc
p-Phenylenediamine, N,N-bis(1,4-dimethylpentyl) (3081-14-9)	A	A	Calc	A
4-Aminodiphenylamine derivatives				
p-Phenylenediamine, N-Isopropyl-N'-phenyl-, (101-72-4)	Calc	A	Calc	A
p-Phenylenediamine, N-(1,3-dimethylbutyl) N'-phenyl (793-24-8)	Calc	A	Calc	A
1,4-Benzenediamine, N,N'-mixed Ph and toyl derivatives (68953-84-4)	R	R	R	A
p-Phenylenediamine, N-(1,4-dimethylpentyl) N'-phenyl (3081-01-4)	Calc	A	Calc	A
p-Phenylenediamine, N,(1methylheptyl)-N'-phenyl, (15233-47-3)	Calc	R	Calc	Calc

Legend	
Symbol	**Description**
R	Endpoint requirement fulfilled using category approach, SAR
Test	Endpoint requirements to be fulfilled with testing
Calc	Endpoint requirement fulfilled based on calculated data
A	Endpoint requirement fulfilled with adequate existing data
NR	Not required per the OECD SIDS guidance
NA	Not applicable due to physical/chemical properties

Table 8 (continued)

CHEMICAL	Ecotoxicity		
	Acute Toxicity to Fish	Acute Toxicity to Aquatic Plants (e.g., Algae)	Acute Toxicity to Aquatic Invertebrates (e.g., Daphnia)
Alkylated N-PPD			
p-Phenylenediamine, N,N-di-sec-butyl (101-96-2)	A	R	A
p-Phenylenediamine, N,N-bis(1,4-dimethylpentyl) (3081-14-9)	A	A	A
4-Aminodiphenylamine derivatives			
p-Phenylenediamine, N-Isopropyl-N'-phenyl-, (101-72-4)	A	A	A
p-Phenylenediamine, N-(1,3-dimethylbutyl) N'-phenyl (793-24-8)	A	A	A
1,4-Benzenediamine, N,N'-mixed Ph and toyl derivatives (68953-84-4)	A	A	A
p-Phenylenediamine, N-(1,4-dimethylpentyl) N'-phenyl (3081-01-4)	A	A	A
p-Phenylenediamine, N,(1methylheptyl)-N'-phenyl, (15233-47-3)	R	R	R

Legend	
Symbol	**Description**
R	Endpoint requirement fulfilled using category approach, SAR
Test	Endpoint requirements to be fulfilled with testing
Calc	Endpoint requirement fulfilled based on calculated data
A	Endpoint requirement fulfilled with adequate existing data
NR	Not required per the OECD SIDS guidance
NA	Not applicable due to physical/chemical properties

Table 8 (continued)

CHEMICAL	Mammalian Toxicity						
	Acute Toxicity	**Genetic Toxicity *In Vitro (bacterial)***	**Genetic Toxicity *In Vitro (mammalian)***	**Genetic Toxicity *In Vivo***	**Repeat Dose Toxicity**	**Repro-ductive Toxicity**	**Develop-mental Toxicity**
Alkylated N-PPD							
p-Phenylenediamine, N,N-di-sec-butyl (101-96-2)	A	A	A	NR	A	R	R
p-Phenylenediamine, N,N-bis(1,4-dimethylpentyl) (3081-14-9)	A	A	A	NR	A	A	A
4-Aminodiphenylamine derivatives							
p-Phenylenediamine, N-Isopropyl-N'-phenyl-, (101-72-4)	A	A	A	R	A	R	A
p-Phenylenediamine, N-(1,3-dimethylbutyl) N'-phenyl (793-24-8)	A	A	A	A	A	A	A
1,4-Benzenediamine, N,N'-mixed Ph and toyl derivatives (68953-84-4)	A	A	A	A	A	A	A
p-Phenylenediamine, N-(1,4-dimethylpentyl) N'-phenyl (3081-01-4)	A	A	R	A	A	R	R
p-Phenylenediamine, N,(1methylheptyl)-N'-phenyl, (15233-47-3)	A	A	R	R	R	R	R

Legend	
Symbol	**Description**
R	Endpoint requirement fulfilled using category approach, SAR
Test	Endpoint requirements to be fulfilled with testing
Calc	Endpoint requirement fulfilled based on calculated data
A	Endpoint requirement fulfilled with adequate existing data
NR	Not required per the OECD SIDS guidance
NA	Not applicable due to physical/chemical properties

AR201-13383B

101-96-2
p-Phenylenediamine, N,N'-di-sec-Butyl

2. PHYSICAL-CHEMICAL DATA

*2.1 MELTING POINT

Value:	18°C
Decomposition:	Yes [ ] No [X] Ambiguous [ ]
Sublimation:	Yes [ ] No [X] Ambiguous [ ]
Method:	Not determined
GLP:	Yes [ ] No [ ] ? [X]
Remarks:	HSDB, NTP Chemical Repository
Reference:	Ashford's Dictionary of Industrial Chemicals, 1994

*2.2 BOILING POINT

Value:	98°C
Pressure:	at 26.6 hPa
Decomposition:	Yes [ ] No [X] Ambiguous [ ]
Method:	Not determined
GLP:	Yes [ ] No [ ] ? [X]
Remarks:	HSDB
Reference:	Kirk-Othmer Encyclopedia of Chemical Technology, 1991

†2.3 DENSITY (relative density)

Type:	Bulk density [X]; Density []; Relative Density [ ]
Value:	0.94 kg/l
Temperature:	20°C
Method:	Not Determined
GLP:	Yes [ ] No [ ] ? [X]
Remarks:	HSDB
Reference:	Ashford's Dictionary of Industrial Chemicals, 1994

*2.4 VAPOUR PRESSURE

Value:	85.3 mm Hg
Temperature:	38°C
Method:	calculated [ ]; measured [X] Instrumental method
GLP:	Yes [ ] No [ ] ? [X]
Remarks:	Radian Research
Reference:	NTP Chemical Repository, 2001

*2.5 PARTITION COEFFICIENT $\log_{10}P_{ow}$

Log Pow:	3.50
Temperature:	Not determined
Method:	calculated [X]; measured [ ] SRC LogKow (KowWin) Program 1995
GLP:	Yes [ ] No [ ] ? [X]
Remarks:	
Reference:	Meylan, W.M. and. P.H. Howard, 1995 J. Pharm. Sci. 84: 83-92

*2.6 WATER SOLUBILITY

A. Solubility

Value:	<1 mg/ml
Temperature:	20°C
Description:	Miscible **[ ]**; Of very high solubility **[ ]**; Of high solubility **[ ]**; Soluble **[ ]**; Slightly soluble **[ ]**; Of low solubility **[ ]**; Of very low solubility **[ ]**; Not soluble **[X]**
Method:	Not determined
GLP:	Yes **[ ]** No **[ ]** ? **[X]**
Remarks:	Radian Research
Reference:	NTP Chemical Repository, 2001

B. pH Value, pKa Value

pH Value:	. . . . .
Concentration:	. . . . .
Temperature:	. . . . . °C
Method:.	
GLP:	Yes **[ ]** No **[ ]** ? **[ ]**
pKa value	. . . . . at 25°C
Remarks:	
Reference:	

2.11 OXIDISING PROPERTIES

Results:	Maximum burning rate equal or higher than reference mixture**[]**; Vigorous reaction in preliminary test **[ ]**; No oxidising properties **[ ]**; Other **[ ]**
Method:	
GLP:	Yes **[ ]** No **[ ]** ? **[ ]**
Remarks:	
Reference:	

†2.12 OXIDATION: REDUCTION POTENTIAL

Value:	. . . . . mV
Method:	
GLP:	Yes **[ ]** No **[ ]** ? **[ ]**
Remarks:	
Reference:	

2.13 ADDITIONAL DATA

A. Partition co-efficient between soil/sediment and water (Kd)

Value:	. . . . .
Method:	
GLP:	Yes **[ ]** No **[ ]** ? **[ ]**
Remarks:	
Reference:	

B. Other data

Results:	
Remarks:	
Reference:	

3. <u>ENVIRONMENTAL FATE AND PATHWAYS</u>

***3.1.1 PHOTODEGRADATION**

Type: Air **[X]**; Water **[ ]**; Soil **[ ]**; Other **[ ]**
Light source: Sunlight **[ ]**; Xenon lamp **[ ]**; Other **[ ]**
Light spectrum: . . . . . nm
Relative intensity: . . . . . *(based on intensity of sunlight)*
Spectrum of substance: . . . . . nm
Concentration of Substance: . . . . . .
Temperature: . . . . . °C
Direct photolysis:
Half life: . . . . . .
Degradation: . . . . . % (weight/weight) after . . . . . (exposure time)
Quantum yield: . . . . . .
Indirect Photolysis:
Type of sensitizer: . . . . . OH . .
Concentration of sensitizer: . 1560000 . . . molecule/cm^3. . . . . .
Rate constant (radical): . . . 117.2377 E-12 .. cm^3/ molecule *sec
Degradation: . . . . . 50% at 1.095 Hrs. . . .
Method: calculated **[X]**; AOP Program (v1.89)
measured **[ ]**

GLP: Yes **[ ]** No **[X]** ? **[ ]**
Test substance: . molecular structure, purity:. . . . . .
Remarks:
Reliability: (2) valid with restrictions
Accepted calculation method
Reference: Meylan W. and Howard P. (1999) EPIWin Modeling Program. Syracuse Research Corporation. Environmental Science Center, 6225 Running Ridge Road, North Syracuse, NY 13212-2510.

***3.1.2 STABILITY IN WATER**

Type: Abiotic (hydrolysis) **[ ]**; biotic (sediment)**[ ]**
Half life: . . . . . at pH . . . . . at . . . . . °C
Degradation: . . . . . at pH . . . . . at . . . . . °C after . . . . . (exposure time)
Method:
GLP: Yes **[ ]** No **[ ]** ? **[ ]**
Test substance: . . . . . , purity: . . . . . .
Remarks:
Reference:

***3.2 MONITORING DATA (ENVIRONMENTAL)**

Type of Measurement: Background **[ ]**; At contaminated site **[ ]**; Other **[ ]**
Media:
Results:
Remarks:
Reference:

3.3 TRANSPORT AND DISTRIBUTION BETWEEN ENVIRONMENTAL COMPARTMENTS INCLUDING ESTIMATED ENVIRONMENTAL CONCENTRATIONS AND DISTRIBUTION

3.4

***3.3.1 TRANSPORT**

Type: Adsorption **[ ]**; Desorption **[ ]**; Volatility **[ ]**; Other **[ ]**
Media:
Method:
Results:
Remarks:
Reference:

***3.3.2 THEORETICAL DISTRIBUTION (FUGACITY CALCULATION)**

Media: Air-biota **[ ]**; Air-biota-sediment-soil-water **[ ]**; Soil-biota **[ ]**; Water-air **[ ]**; Water-biota **[ ]**; Water-soil **[ ]**; Other **[ ]**

Method: Fugacity level I **[ ]**; Fugacity level II **[ ]**; Fugacity level III **[X]**; Fugacity level IV**[]**;Other (calculation)**[]**;Other (measurement)**[ ]**

Results:

	Concentration (percent)	Half-Life (hr)	Emissions (kg/hr)	Fugacity (atm)
Air	0.0952	2.19	1000	2.37e-012
Water	26.1	900	1000	2.36e-013
Soil	72.6	900	1000	2.33e-013
Sediment	1.24	3.6e+003	0	1.75e-013

	Reaction (kg/hr)	Advection (kg/hr)	Reaction (percent)	Advection (percent)
Air	678	21.4	22.6	0.714
Water	451	586	15	19.5
Soil	1.26e+003	0	41.9	0
Sediment	5.35	0.556	0.178	0.0185

Persistence Time: 750 hr
Reaction Time: 940 hr
Advection Time: 3.7e+003 hr
Percent Reacted: 79.7
Percent Advected: 20.3

Remarks:
Reliability: (2) valid with restrictions
Accepted calculation method
Reference: Meylan W. and Howard P. (1999) EPIWin Modeling Program. Syracuse Research Corporation. Environmental Science Center, 6225 Running Ridge Road, North Syracuse, NY 13212-2510.

***3.5 BIODEGRADATION**

Type: aerobic **[ ]**; anaerobic **[ ]**
Inoculum: adapted **[ ]**; non-adapted **[ ]**;
Concentration of the chemical: . . . . . related to COD **[ ]**; DOC **[ ]**; test substance **[ ]**
Medium: water **[ ];** water-sediment **[ ];** soil **[ ];** sewage treatment **[ ]**
Degradation: *(percentage reduction/exposure time)*
. . . . . % after . . . . . (time)
Results: readily biodeg. **[ ];** inherently biodeg. **[ ]**; under test condition no biodegradation observed **[ ]**, other **[ ]**
Kinetic . . . . . % in . . . . . (time)
Method:
GLP: Yes **[ ]** No **[ ]** ? **[ ]**
Test substance: . . . . . , purity: . . . . . .

Remarks:
Reference:

4. ECOTOXICITY

*4.1 ACUTE/PROLONGED TOXICITY TO FISH

Type of test: static **[X]**; semi-static **[ ]**; flow-through **[ ]**; other **[ ]**
open-system **[ ]**; closed-system **[X]**
Species: Salmo gairdneri (Rainbow Trout)
Exposure period: 96 Hours
Results: LC_{50} (24h) = >0.18 mg/l
LC_{50} (48h) = 0.14 mg/l
LC_{50} (72h) = Not determined
LC_{50} (96h) = 0.13 mg/l
NOEC = 0.056 mg/l
LOEC = 0.10 mg/l
Analytical monitoring: Yes **[X]** No **[ ]** ? **[ ]**
Method: EPA Methods for Acute Toxicity Tests with Fish, Macroinvertebrates and Amphibians (1975)
GLP: Yes **[X]** No **[ ]** ? **[ ]** **Klimisch 1**
Test substance:. Santoflex 44 dark red liquid #KB12-902, purity: >97%
Remarks: Acetone used as solvent. Range-finding experiment conducted to determine final bioassay test concentrations. Water temperature, dissolved oxygen content, and pH monitored throughout study. Quality check via challenge with reference compound Antimycin A. Data reported at 95% confidence level.
Reference: Monsanto AB-83X-036, Analytical Bio-Chemistry Labs, 1983

Type of test: static **[X]**; semi-static **[ ]**; flow-through **[ ]**; other **[ ]**
open-system **[ ]**; closed-system **[X]**
Species: Lepomis machrochirus (Bluegill Sunfish)
Exposure period: 96 Hours
Results: LC_{50} (24h) = 0.19 mg/l
LC_{50} (48h) = 0.18 mg/l
LC_{50} (72h) = Not determined
LC_{50} (96h) = 0.18 mg/l
NOEC = 0.10 mg/l
LOEC = 0.18 mg/l
Analytical monitoring: Yes **[X]** No **[ ]** ? **[ ]**
Method: EPA Methods for Acute Toxicity Tests with Fish, Macroinvertebrates and Amphibians (1975)
GLP: Yes **[X]** No **[ ]** ? **[ ]** **Klimisch 1**
Test substance:. Santoflex 44 dark red liquid #KB12-902, purity: >97%
Remarks: Acetone used as solvent. Range-finding experiment conducted to determine final bioassay test concentrations. Water temperature, dissolved oxygen content, and pH monitored throughout study. Quality check via challenge with reference compound Antimycin A. Data reported at 95% confidence level.
Reference: Monsanto AB-83X-035, Analytical Bio-Chemistry Labs, 1983

Type of test: static **[X]**; semi-static **[ ]**; flow-through **[ ]**; other **[ ]**
open-system **[ ]**; closed-system **[X]**
Species: Pimephales promelas (Fathead Minnows)
Exposure period: 96 Hours
Results: LC_{50} (24h) = 0.13 mg/l
LC_{50} (48h) = 0.13 mg/l
LC_{50} (72h) = Not determined
LC_{50} (96h) = 0.13 mg/l
NOEC = 0.10 mg/l
LOEC = 0.18 mg/l
Analytical monitoring: Yes **[X]** No **[ ]** ? **[ ]**
Method: EPA Methods for Acute Toxicity Tests with Fish, Macroinvertebrates and Amphibians (1975)
GLP: Yes **[X]** No **[ ]** ? **[ ]** **Klimisch 1**
Test substance:. Santoflex 44 dark red liquid #KB12-902, purity: >97%
Remarks: Acetone used as solvent. Range-finding experiment conducted to determine final bioassay test concentrations. Water temperature, dissolved oxygen content, and pH monitored throughout study. Quality check via challenge with reference compound Antimycin A. Data reported at 95% confidence level.
Reference: Monsanto AB-84X-021, Analytical Bio-Chemistry Labs, 1983

4.2 ACUTE TOXICITY TO AQUATIC INVERTEBRATES

*A. Daphnia

Type of test: static **[X]**; semi-static **[ ]**; flow-through **[ ]**; other **[ ]**;
open-system **[ ]**; closed-system **[X]**
Species: Daphnia magna
Exposure period: 48 Hours
Results: EC_{50} (24h) = 2.0 mg/l
EC_{50} (48h) = 1.4 mg/l
NOEC = 0.56 mg/l
Analytical monitoring: Yes **[X]** No **[ ]** ? **[ ]**
Method: EPA Methods for Acute Toxicity Tests with Fish, Macroinvertebrates and Amphibians (1975)
GLP: Yes **[X]** No **[ ]** ? **[ ]** **Klimisch 1**
Test substance: Santoflex 44 dark liquid Lot# KB12-902, purity:>97%
Remarks: Acetone used as solvent. Range-finding experiment conducted to determine final bioassay test concentrations. Water temperature, dissolved oxygen content, and pH monitored throughout study. The abnormal effects of mortality and daphnids lying on the bottom progressed from 3.2 mg/l initially, to 1.0 mg/l after 48 hours.
Reference: Monsanto AB-83X-037, Analytical Bio-Chemistry Labs, 1983

*4.3 TOXICITY TO AQUATIC PLANTS, e.g. algae

Species:
Endpoint: Biomass **[ ]**; Growth rate **[ ]**; Other **[ ]**
Exposure period:
Results: EC_{50} (. . . . . .h) = ... mg/l
EC_{xx} (. . . . . .h) = ... mg/l

NOEC = ... mg/l
LOEC = ... mg/l
Analytical monitoring: Yes **[ ]** No **[ ]** ? **[ ]**
Method:
open-system **[ ]**; closed-system **[ ]**
GLP: Yes **[ ]** No **[ ]** ? **[ ]**
Test substance: . . . . . , purity: . . . . . .
Remarks:
Reference:

5. TOXICITY

*5.1 ACUTE TOXICITY

5.1.1 ACUTE ORAL TOXICITY

Type: LD_0 **[ ]**; LD_{100} **[ ]**; LD_{50} **[X]**; LDL_0 **[ ]**; Other **[ ]**
Species/strain: Sprague-Dawley Albino Rats
Value: 271 mg/kg bw for males and females combined
281 mg/kg for males
265 mg/kg for females
Method: Finney, J.D., Reference for Method of LD50 Determination, Probit Analysis 3rd Edition, 1971
GLP: Yes **[X]** No **[ ]** ? **[ ]** **Klimisch 1**
Test substance: Santoflex 44, Lot S-40182, purity: 96.09%
Remarks: Groups of five male and five female rats were dosed by oral gavage with the test article as a 392 mg/ml solution in corn oil. Clinical observations were made 3x/day during the first 8 hours, and 2x/day thereafter until sacrifice. After a 14-day recovery period, all surviving animals were sacrificed. Necropsies were performed on all animals. Clinical signs of toxicity included lethargy, ataxia, ptosis, and abnormal urine coloration (green and/or reddish-brown). Necropsy findings included gastrointestinal inflammation, which reached the severity of hemmorhage in many cases, gastrointestinal distension, and red, fluid-filled gastric masses. The presence of these masses indicated that the toxicity to gastrointestinal tissue may have contributed to lethality in virtually all rats that died during the test. Previous oral and dermal toxicity studies with this material have noted the corrosivity to tissue that complicates accurate determinations of LD50 values.
Reference: Monsanto ML-82-181, Environmental Health Labs, 1983

5.1.2 ACUTE INHALATION TOXICITY

Type: LC_0 **[ ]**; LC_{100} **[ ]**; LC_{50} **[ ]**; LCL_0 **[X]**; Other **[ ]**
Species/strain: Sprague-Dawley Albino Rats
Exposure time: 6 Hours
Value: 600 mg/m3
Method: Not Determined
GLP: Yes **[ ]** No **[ ]** ? **[X]** **Klimisch 2**
Test substance:. Cas # 101-96-2, purity: Commercial (>96%)
Remarks: RTECS and NTP reference. Test conditions unknown.
Reference: Kodak Company Reports, 1971

Type:	LC_0 **[ ]**; LC_{100} **[ ]**; LC_{50} **[X]**; LCL_0 **[ ]**; Other **[ ]**
Species/strain:	Sprague-Dawley Albino Male Rats
Exposure time:	6 Hours
Value:	>0.2 mg/l
Method:	A.T.S. 8/1973
GLP:	Yes **[ ]** No **[X]** ? **[ ]** **Klimisch 2**
Test substance:.	Santoflex 44 Lot# 24277, purity: >96%
Remarks:	Six male rats were exposed to the test article at a concentration of 0.2 mg/l at ambient temperature at an airflow rate of 4 l/min for six hours. The difference in weight of the sample after the test indicated that 0.4 grams had been vaporized under test conditions. There were no clinical signs of toxicity noted during the experiment. Following a 14-day recovery period, all animals were sacrificed. Necropsy findings were that all viscera examined appeared normal.
Reference:	Monsanto Y-76-262, Younger Laboratories, 1976

5.1.3 ACUTE DERMAL TOXICITY

Type:	LD_0 **[ ]**; LD_{100} **[ ]**; LD_{50} **[X]**; LDL_0 **[ ]**; Other **[ ]**
Species/strain:	New Zealand Albino Rabbits
Value:	2806 mg/kg bw
Method:	Finney, J.D., Reference for Method of LD50 Determination, Probit Analysis 3rd Edition, 1971
GLP:	Yes **[X]** No **[ ]** ? **[ ]** **Klimisch 1**
Test substance:	Santoflex 44 Lot S-40182, purity: 96.09%
Remarks:	Groups of four male and female rabbits were exposed to the test article via a single dermal application to shaved skin. Two animals from each group were predesignated to have their skin abraided in the treatment area. Skin of the other animals was intact. Clinical observations were made 3x/day during the first eight hours after exposure, then 2x/day thereafter until sacrifice. Necropsies were performed on all animals. Clinical signs of toxicity included lethargy, ataxia, green coloration of the urine, partial loss of ability to move the limbs, and localized dermal effects attributed to the direct contact between skin and test article. Findings on necropsy included green material in the bladder of sixteen animals, four animals with an enlarged gall bladder, and five with hepatic discoloration.
Reference:	Monsanto ML-82-022, Environmental Health Lab, 1983

5.2 CORROSIVENESS/IRRITATION

5.2.1 SKIN IRRITATION/CORROSION

Species/strain:	New Zealand White Rabbits
Results:	Highly corrosive **[ ]**; Corrosive **[X]**; Highly irritating **[ ]**; Irritating **[ ]**; Moderate irritating **[ ]**; Slightly irritating **[x]**; Not irritating **[ ]**
Classification:	Highly corrosive (causes severe burns) **[ ]**; Corrosive (causes burns) **[X]**; Irritating **[ ]**; Not irritating **[ ]**
Method:	Draize, J.H. Woodard, G., and Calvery, H.O., Methods for the Study of Irritation and Toxicity of Substances Applied Topically

To the Skin and Mucous Membranes, J. Pharmacol. Exp. Therap. 82: 377-390, 1944

GLP: Yes **[X]** No **[ ]** ? **[ ]** **Klimisch 1**

Test substance: Santoflex 44 Lot S-40182, purity: 96.09%

Remarks: The test undiluted article, at a volume of 0.5 ml, was applied to the intact and abraided shaved skin of six rabbits for 24 hours. The initial observation was made approximately one hour after exposure. Dermal irritation was scored by the Draize Method, and results recorded on day 1, 3, 7, 10, 14 and 17 after exposure. Scarring, hardening of the skin, scabbing and sloughing skin were noted on all animals. The test article was classified as corrossive under the test conditions.

Reference: Monsanto ML-82-022c, Environmental Health Lab, 1983

SKIN IRRITATION/CORROSION

Species/strain: New Zealand Albino Rabbits

Results: Highly corrosive **[ ]**; Corrosive **[ ]**; Highly irritating **[X]**; Irritating **[ ]**; Moderate irritating **[ ]**; Slightly irritating **[ ]**; Not irritating **[ ]**

Classification: Highly corrosive (causes severe burns) **[ ]**; Corrosive (causes burns) **[ ]**; Irritating **[X]**; Not irritating **[ ]**

Method: D.O.T. Hazardous Material Regulations 49 CFR 173.240, 1976

GLP: Yes **[X]** No **[ ]** ? **[ ]** **Klimisch 1**

Test substance:. Antioxidant PDA #1549-83, purity: Not stated

Remarks: The undiluted test article was applied to the shaved skin of six rabbits in a single application of 0.5 ml. The test site was covered for four hours with surgical gauze and an elastic bandage. The entire trunk of the rabbit was wrapped in 2 mil thick plastic to prevent evaporation of the test article, and the plastic was covered with a white cotton towel. After four hours, the wrappings were removed, and the skin allowed to equilibrate for hydration and compression for 30 minutes. Skin was scored for erythema, eschar formation and corrosion in accordance with the Federal Hazardous Substances Act Grading Code, 16 CFR 1500.41. After grading, the test site was washed with water. Test sites were scored again after 24, 48 and 72 hours, and 1 and 2 weeks. Gross observations of corrosion were noted in 2/6 rabbits at I week and in 4/6 rabbits after 2 weeks. Under the conditions of the DOT test, these results were judged to be between "marginal" and "severely irritating but not corrosive". Because of the results of earlier studies, the manufacturers of this material have chosen to classify it as "corrosive" for both use and transportation.

Reference: Monsanto XX-84X-144, Gulf South Research, 1983

5.2.2 EYE IRRITATION/CORROSION

Species/strain: New Zealand Albino Rabbits

Results: Highly corrosive **[ ]**; Corrosive **[X]**; Highly irritating **[ ]**; Irritating **[ ]**; Moderate irritating **[ ]**; Slightly irritating **[ ]**; Not irritating **[ ]**

Classification: Irritating **[]**; Not irritating **[]**; Risk of serious damage to eyes **[X]**

Method: Draize et.al., J. Pharmacol., Exp. Therap. 82: pp 377-390, 1944

GLP: Yes **[ ]** No **[ ]** ? **[x]**

Test substance:. Santoflex 44 Lot# S-40182, purity 96.09%

Remarks: A single dose of 0.1 ml of the undiluted test article was placed in the one eye of three male and three female rabbits, with the untreated eye serving as the control. A topical anesthetic available if discomfort appeared severe. Signs of irritation were scored according to the Draize procedure. Scoring will be done at 24, 48 and 72 hours after treatment. Discomfort on application was slight. Observations at 24 hours included severe erythema with necrosis, severe edema, copious discharge containing a whitish exudate and severe swelling of conjunctivae. Under the test conditions, the material was classified as "corrosive". Scabs sloughed off in 14 to 21 days with no apparent permanent corneal damage.

Reference: Monsanto ML-82-022d, Environmental Health Laboratory, 1983

***5.4 REPEATED DOSE TOXICITY**

Species/strain: Sprague-Dawley Albino Rats

Sex: Female **[ ]**; Male **[ ]**; Male/Female **[X]**; No data **[ ]**

Route of Administration: Oral gavage

Exposure period: 28 days

Frequency of treatment: Daily

Post exposure observation period:

Dose: 0, 10, 25, 50, or 100 mg/kg

Control group: Yes **[X]**; No **[ ]**; No data **[ ]**;
Concurrent no treatment **[]**; Concurrent vehicle **[X]**; Historical **[]**

NOEL: <10 mg/kg

LOEL: 10 mg/kg

Results: 100 male and female rats (10/sex/dose level) were dosed with the test article in corn oil vehicle at the above levels for a period of 28 days. The animals were observed 2x/day for mortality or signs of toxicity. Detailed observations, body weights and feed consumption was documented 1x/week. Hematology determinations and clinical chemistry determinations were made on all control animals and the high-dose animals prior to terminal sacrifice. Additional clinical chemistry determinations of GGTP, SGOT, Sgtp, Bilirubin, SAP and 5-nucleotidase were performed on all treated animals. A complete gross necropsy was performed on all animals at sacrifice and within 16 hours of any animal who died during the course of the study. Two mid-dose males died within the first week of treatment and two high-dose females died during week 3. Cause of death did not appear to be treatment-related. One additional mid-dose female was sacrificed at day 15 following an injury during dosing. All other animals survived to sacrifice. Gross necropsy findings on two high-dose females was a slightly pale liver. In males, a finding of dilation of the right renal pelvis was found in several animals at all dose levels, including controls. Adverse effects observed included increased liver weights and elevation of serum enzymes SGOT, Sgpt and GGTP, indicative of hepatocellular damage, as well as a dose-dependent increase in the incidence of hepatocellular lesions. Because the results of this study demonstrated hepatic effects in

both sexes and at all treatment levels, a No Observed Effect Level could not be established.

Method: OECD Guidelines for the Testing of Chemicals, 1981
GLP: Yes **[X]** No **[ ]** ? **[ ]** **Klimisch 1**
Test substance:. Santoflex 44 Lot# KC11-928, purity: >96%
Reference: Monsanto PR-83-317, Pharmacopathics Research Labs, 1984

Species/strain: Sprague-Dawley Albino Rats
Sex: Female **[ ]**; Male **[ ]**; Male/Female **[X]**; No data **[ ]**
Route of Administration: Oral dietary
Exposure period: 90-94 days
Frequency of treatment: Daily
Post exposure observation period:
Dose: 0, 20, 100 or 500 ppm
Control group: Yes **[X]**; No **[ ]**; No data **[ ]**;
Concurrent no treatment **[X]**; Concurrent vehicle **[]**; Historical **[]**
NOEL: 100 mg/kg
LOEL: 500 mg/kg
Results: In a subchronic feeding study, groups of male and female rats were fed the test article via dietary admixture for three months. After 65 days of treatment, the low-dose (20 ppm) group was increased to 1000 ppm for twenty-five days, and then to 2000 ppm for the final four days of the study. Findings included decreased body weights and body weight gain in the 500 ppm males, and decreased body weights in the 500 ppm females. There were no clinical signs of toxicity noted for any dose level for either sex. All animals survived until terminal sacrifice. Hematology determinations and clinical chemistry determinations were made on all animals prior to sacrifice, and all animals received a complete gross necropsy. There were no hematological or histopathological findings at any dose level that were considered to be treatment-related. The NOEL was determined to be 100 ppm, or 6.6 mg/kg/day, for both males and females based upon the reduced body weights seen at 500 ppm.
Method: Not determined
GLP: Yes **[ ]** No **[ ]** ? **[X]** **Klimisch 2**
Test substance:. Antioxidant 22, purity: Commercial grade, 96% minimum
Reference: E.I. DuPont de Nemours, unpublished data, 1987

*5.5 GENETIC TOXICITY IN VITRO

A. BACTERIAL TEST

Type: Bacterial Reverse Mutation - Ames
System of testing: Salmonella typhimurium TA97, TA98, TA100, TA1535, TA 1537, TA1538
Concentration: Not determined
Metabolic activation: With **[ ]**; Without **[ ]**; With and Without **[X]**; No data **[ ]**
Results:
Cytotoxicity conc: With metabolic activation: Not determined
Without metabolic activation: Not determined

Precipitation conc: Not determined

Genotoxic effects: + ? -

With metabolic activation: **[ ] [ ] [X]**

Without metabolic activation: **[ ] [ ] [X]**

Method: OECD 471 Plate Overlay method

GLP: Yes **[]** No **[ ]** ? **[X]** **Klimisch 2**

Test substance: N,N'-di-sec-butyl-p-phenylenediamine, purity: Technical grade

Remarks: The test compound was tested in Ames/Salmonella plate incorporation assays using the tester strains TA 97, TA98, T A100, TA1535, and TA1538 and TA1537 in the presence and absence of an Aroclor-induced rat liver mammalian metabolic activation system (S-9 Mix). No mutagenic activity was observed for the test compound in any of these assays.

Reference: Zeiger, et. al., Environ. Mol. Mutagen, 1998

B. NON-BACTERIAL IN VITRO TEST

Type: CHO and CHL Forward Gene Mutation Assay

System of testing: Cultured Chinese hamster ovary (CHO) cells and cultured Chinese Hamster Lung (CHL) cells

Concentration: Not determined

Metabolic activation: With **[ ]**; Without **[ ]**; With and Without **[X]**; No data **[ ]**

Results:

Cytotoxicity conc: With metabolic activation: Not determined

Without metabolic activation: Not determined

Precipitation conc: Not determined

Genotoxic effects: + ? -

With metabolic activation (CHO): **[ ] [ ] [X]**

Without metabolic activation (CHO): **[ ] [ ] [X]**

With metabolic activation (CHL): **[ ] [ ] [X]**

Without metabolic activation (CHL): **[ ] [X] [ ]**

Method: OECD 476

GLP: Yes **[ ]** No **[ ]** ? **[X]** **Klimisch 2**

Test substance:. N,N'-di-sec-butyl-p-phenylenediamine, purity: Commercial grade

Remarks: The test article was one of 25 chemicals tested for the induction of chromosomal aberrations in two cultured mammalian cell systems the cultured cells from Chinese hamster ovaries (CHO, and those from Chinese hamster lungs (CHL), in the presence absence of metabolic activation with the S9 mix. The test article negative with metabolic activation in both CHO and CHL cells, and negative without metabolic activation in CHO cells. The results for CHL cells without metabolic activation were equivocal. Overall, the results indicate that the test article is negative for the potential to cause chromosomal aberrations, both with and without metabolic activation, under the test conditions.

Reference: Sofuni, et.al. Mutation Research, 1990

*** 5.6 GENETIC TOXICITY IN VIVO**

Type:

Species/strain:

Sex: Female **[ ]**; Male **[ ]**; Male/Female **[ ]**; No data **[ ]**

Route of Administration:

Exposure period:

Doses:
Results:
Effect on mitotic
index or P/N ratio:
Genotoxic effects: + ? -
[ ] [ ] [ ] [ ]
Method:
GLP: Yes **[ ]** No **[ ]** ? **[ ]**
Test substance: . . . . . , purity: . . . . . .
Remarks:
Reference:

***5.8 TOXICITY TO REPRODUCTION**

Type: Fertility **[]**; One-generation study **[]**; Two-generation study **[]**;
Species/strain:
Sex: Female **[ ]**; Male **[ ]**; Male/Female **[ ]**; No data **[ ]**
Route of Administration:
Exposure period:
Frequency of treatment:
Post exposure observation period:
Premating exposure period: male: . . . . . , female:
Duration of the test:
Doses:
Control group: Yes **[ ]**; No **[ ]**; No data **[ ]**;
Concurrent no treatment **[ ]**; Concurrent vehicle **[ ]**; Historical **[ ]**
NOEL Parental: .
NOEL F1 Offspring:
NOEL F2 Offspring:
Results:
General parental toxicity:
Toxicity to offspring:
Method:
GLP: Yes **[ ]** No **[ ]** ? **[ ]**
Test substance: . . . . . , purity: . . . . . .
Remarks:
Reference:

***5.9 DEVELOPMENTAL TOXICITY/ TERATOGENICITY**

Species/strain:
Sex: Female **[ ]**; Male **[ ]**; Male/Female **[ ]**; No data **[ ]**
Route of Administration: .
Duration of the test:
Exposure period:
Frequency of treatment:
Doses:
Control group: Yes **[ ]**; No **[ ]**; No data **[ ]**;
Concurrent no treatment **[ ]**; Concurrent vehicle **[]**; Historical **[ ]**
NOEL Maternal Toxicity:
NOEL teratogenicity :
Results:
Maternal general toxicity:
Pregnancy/litter data:

Foetal data:

Method:

GLP: Yes **[ ]** No **[ ]** ? **[ ]**

Test substance: . . . . . , purity: . . . . . .

Remarks:

Reference:

5.10 OTHER RELEVANT INFORMATION

A. Specific toxicities

Type:

Results:

Remarks:

Reference:

B. Toxicodynamics, toxicokinetics

Type:

Results:

Remarks:

References:

*** 5.11 EXPERIENCE WITH HUMAN EXPOSURE**

Results: Cyanosis and anemia have been observed in workers involved in the manufacture of Antioxidant 22.

Remarks: Dermal route

Reference: E,I, DuPont de Nemours, 1987

Results: Historically, three incidents involving accidental human overexposure involving Antioxidant 22 have been documented. Skin reactions noted were irritation and a pigmented crust that scaled away in a few days, leaving an erythematous base. Systemic reactions, indicative of skin absorbtion, included profuse perspiration, slow pulse, and a general feeling of anxiety.

Remarks: Data from 1945 does not reflect current industrial practice utilizing Impervious gloves and other personal protective equipment

Reference: Kendrick, M.C., The Medical Bulletin, 1945

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3081-14-9
p-Phenylenediamine, N-1,4-Dimethylpentyl-N'-Phenyl-

2. PHYSICAL-CHEMICAL DATA

*2.1 MELTING POINT

Value:	-36 °C
Decomposition:	Yes **[ ]** No **[X]** Ambiguous **[ ]**
Sublimation:	Yes **[ ]** No **[X]** Ambiguous **[ ]**
Method:	Not Specified
GLP:	Yes **[ ]** No **[ ]** ? **[X]**
Remarks:	
Reference:	NTP Chemical Repository 1990

*2.2 BOILING POINT

Value:	183 °C
Pressure:	1mm Hg
Decomposition:	Yes **[ ]** No **[X]** Ambiguous **[ ]**
Method:	Capillary Melt-Temp Instrument
GLP:	Yes **[ ]** No **[ ]** ? **[X]**
Remarks:	
Reference:	Monsanto Physical Constants of CP25447 (SMP 1977)

†2.3 DENSITY (relative density)

Type:	Bulk density **[ ]**; Density **[X]**; Relative Density **[ ]**
Value:	0.9
Temperature:	27 °C
Method:	Flexsys Standard Method of Analysis FF97.4-1
GLP:	Yes **[ ]** No **[ ]** ? **[X]**
Remarks:	Hydrometer method. Hydrometer must meet standards set in ASTM-E-100
Reference:	ASTM D891-94 method equivalent

*2.4 VAPOUR PRESSURE

Value:	<1.1 x 10(-6) Torr
Temperature:	25°C
Method:	calculated **[ ]**; measured **[X]** Gas Saturation Method, W.F. Spencer and M.M. Cliath, Environ. Sci. Tech. 3, 670 (1969)
GLP:	Yes **[X]** No **[ ]** ? **[ ]**
Remarks:	Nitrogen carrier gas, Tenax-GC sorbent, GC analysis
Reference:	Monsanto SRI 8669, SRI International, 1980

*2.5 PARTITION COEFFICIENT $\log_{10}P_{ow}$

Log Pow:	5.34 log P
Temperature:	22°C
Method:	calculated **[ ]**; measured **[X]** EPA Federal Register Vol. 44, No. 53 (1979)
GLP:	Yes **[X]** No **[ ]** ? **[ ]**
Remarks:	Octanol used as solvent
Reference:	Monsanto SRI 8669, SRI International, 1980

***2.6 WATER SOLUBILITY**

A. Solubility

Value:	21 ppm @ pH 5, 0.8 ppm @ pH 9
Temperature:	22°C
Description:	Miscible **[ ]**; Of very high solubility **[ ]**;
	Of high solubility **[ ]**; Soluble **[ ]**; Slightly soluble **[ ]**;
	Of low solubility **[ ]**; Of very low solubility[**X]**; Not soluble **[ ]**
Method:	May, W.E., Wasik, S.P., Freeman, D.H., Anal. Chem. 50 (1) 175-178, 1978
GLP:	Yes **[X]** No **[ ]** ? **[ ]**
Remarks:	May Method chosen for low-solubility chemicals
Reference:	Monsanto SRI 8669, SRI International, 1980

B. pH Value, pKa Value

pH Value:	Not Applicable

2.7 FLASH POINT *(liquids)*

Value:	182 °C
Type of test:	Closed cup **[ ]**; Open cup **[X]**; Other **[ ]**
Method:	ASTM D 92 Cleveland Open Cup
GLP:	Yes **[X]** No **[ ]** ? **[ ]** **Klimisch 1**
Remarks:	No method deviations
Reference:	American Society for Testing and Materials, 1997

2.13 ADDITIONAL DATA

A. Partition co-efficient between soil/sediment and water (Kd)

Value:	
Method:	
GLP:	Yes **[ ]** No **[ ]** ? **[ ]**
Remarks:	
Reference:	

3. ENVIRONMENTAL FATE AND PATHWAYS

3.1 STABILITY

***3.1.1 PHOTODEGRADATION**

Type:	Air **[ ]**; Water **[X]**; Soil **[ ]**; Other **[ ]**
Light source:	Sunlight **[X]**; Xenon lamp **[ ]**; Other **[ ]**
Light spectrum:	Natural sunlight, March 7, 1980
Relative intensity:	
Spectrum of substance:	*262* nm
Concentration of Substance:	5ppm
Temperature:	23 °C
Direct photolysis:	
Half life:	2 hours (light) and 4 hours (dark)
Degradation:	
Quantum yield:	
Method:	calculated **[ ]**; measured **[X]**

Direct Photolysis
GLP: Yes **[ ]** No **[ ]** ? **[X]** **Klimisch 2**
Test substance: Santoflex 77 dark liquid, purity: >94%
Remarks:
Reference: Monsanto SR-85-017 SRI International, 1985

Type: Air **[X]**; Water **[ ]**; Soil **[ ]**; Other **[ ]**
Light source: Sunlight **[ ]**; Xenon lamp **[ ]**; Other **[ ]**
Light spectrum: . . . . . nm
Relative intensity: . . . . . *(based on intensity of sunlight)*
Spectrum of substance: . . . . . nm
Concentration of Substance: . . . . . .
Temperature: . . . . . °C
Direct photolysis:
Half life: . . . . . .
Degradation: . . . . . % (weight/weight) after . . . . . (exposure time)
Quantum yield: . . . . . .
Indirect Photolysis:
Type of sensitizer: . . . . . .OH . . .
Concentration of sensitizer: . . 1560000 . . molecule/. cm^3 . . . . .
Rate constant (radical): . . . 125.6992 E-12. . . cm^3/molecule*sec
Degradation: . . . 50% at 1.021 Hrs. . . . . .
Method: calculated **[X]**; AOP Program (v1.89)
measured **[ ]**
GLP: Yes **[ ]** No **[X]** ? **[ ]**
Test substance: . molecular structure. . . . . , purity:. . . . . .
Remarks:
Reliability: (2) valid with restrictions
Accepted calculation method
Reference: Meylan W. and Howard P. (1999) EPIWin Modeling Program. Syracuse Research Corporation. Environmental Science Center, 6225 Running Ridge Road, North Syracuse, NY 13212-2510.

***3.1.2 STABILITY IN WATER**

Type: Abiotic (hydrolysis) **[X]**; biotic (sediment)**[ ]**
Half life: Not measured
Degradation: 97% at pH 7.0 at 25 °C after 24 hours exposure time
Method: Phase I Hydrolysis Study / ID of Hydrolysis Products
GLP: Yes **[X]** No **[ ]** ? **[ ]** **Klimisch 1**
Test substance: Santoflex 77 dark reddish liquid, purity: >94%
Remarks: Rapid hydrolysis to 4-Hydroxylamine and Benzoquinoneimine-N-phenyl. No test substance detected after 7 days.
Reference: Monsanto ABC-32303 Analytical BioChemistry Labs 1986

***3.3.2 THEORETICAL DISTRIBUTION (FUGACITY CALCULATION)**

Media: Air-biota **[ ]**; Air-biota-sediment-soil-water **[ ]**; Soil-biota **[ ]**; Water-air **[ ]**; Water-biota **[ ]**; Water-soil **[ ]**; Other **[ ]**
Method: Fugacity level I **[ ]**; Fugacity level II **[ ]**; Fugacity level III **[X]**; Fugacity level IV **[ ]**; Other (calculation) **[ ]**; Other (measurement)**[ ]**

Results:

	Concentration (percent)	Half-Life (hr)	Emissions (kg/hr)	Fugacity (atm)
Air	0.0609	2.04	1000	2.1e-012
Water	5.53	900	1000	1.65e-013
Soil	31.7	900	1000	1.25e-015
Sediment	62.7	3.6e+003	0	1.11e-013

	Reaction (kg/hr)	Advection (kg/hr)	Reaction (percent)	Advection (percent)
Air	901	26.6	30	0.885
Water	186	241	6.19	8.04
Soil	1.06e+003	0	35.5	0
Sediment	527	54.7	17.6	1.82

Persistence Time: 1.45e+003 hr
Reaction Time: 1.63e+003 hr
Advection Time: 1.35e+004 hr
Percent Reacted: 89.3
Percent Advected: 10.7

Remarks:
Reliability: (2) valid with restrictions
Accepted calculation method
Reference: Meylan W. and Howard P. (1999) EPIWin Modeling Program. Syracuse Research Corporation. Environmental Science Center, 6225 Running Ridge Road, North Syracuse, NY 13212-2510.

***3.5 BIODEGRADATION**

Type: aerobic **[X]**; anaerobic **[ ]**
Inoculum: adapted **[X]**; non-adapted **[ ]**; Sewage/soil/sludge mixture
Concentration of the chemical: 25 mg/l related to COD **[ ]**; DOC **[ ]**; test substance **[X]**
Medium: water **[];** water-sediment **[];** soil **[];** sewage treatment **[X]**
Degradation: 50% of theory after 35 days
Results: readily biodeg. **[];** inherently biodeg. **[X]**; under test condition no biodegradation observed **[ ]**, other **[ ]**
Kinetic . . . . . % in . . . . . (time)
Method: ASTM Proposed Standard for the Determination of the Ultimate Biodegradability of Organic Chemicals, 1979
GLP: Yes **[ ]** No **[ ]** ? **[X]** **Klimisch 2**
Test substance: Santoflex 77 Lot# KL01-04, purity:>94%
Remarks: Sterile controls used – no significant biodegradation noted under sterile conditions. Test run in triplicate.
Reference: Monsanto ES-79-SS-25 MIC Environmental Sciences, 1979

4. ECOTOXICITY

***4.1 ACUTE/PROLONGED TOXICITY TO FISH**

Type of test: static **[X]**; semi-static **[]**; flow-through **[ ]**; other *(e.g. field test)* **[ ]**
open-system **[ ]**; closed-system **[X]**
Species: Salmo gairdneri (Rainbow Trout)
Exposure period: 96 hours
Results: LC_{50} (24h) = 51 mg/l

LC_{50} (48h) = 39 mg/l
LC_{50} (72h) = Not Measured
LC_{50} (96h) = 32 mg/l
NOEC = 20 mg/l
LOEC = 32 mg/l

Analytical monitoring: Yes **[X]** No **[ ]** ? **[ ]**

Method: EPA Methods for Acute Toxicity Tests with Fish, Macroinvertebrates and Amphibians (1975)

GLP: Yes **[ ]** No **[ ]** ? **[X]** **Klimisch 1**

Test substance:. Santoflex 77 dark red liquid Lot #KD05-57 purity:>94%

Remarks: Acetone used as solvent. Water temperature, dissolved oxygen content, and pH monitored throughout study. Data reported at 95% confidence level.

Reference: Monsanto BN-76-254 EG&G Bionomics, 1976

Type of test: static **[X]**; semi-static **[]**; flow-through **[ ]**; other *(e.g. field test)* **[ ]** open-system **[ ]**; closed-system **[X]**

Species: Lepomis machrochirus (Bluegill Sunfish)

Exposure period: 96 hours

Results:
LC_{50} (24h) = 261 mg/l
LC_{50} (48h) = 201 mg/l
LC_{50} (72h) = Not Measured
LC_{50} (96h) = 182 mg/l
NOEC = 140 mg/l
LOEC = 180 mg/l

Analytical monitoring: Yes **[X]** No **[ ]** ? **[ ]**

Method: EPA Methods for Acute Toxicity Tests with Fish, Macroinvertebrates and Amphibians (1975)

GLP: Yes **[ ]** No **[ ]** ? **[X]** **Klimisch 1**

Test substance:. Santoflex 77 dark red liquid Lot #KD05-57 purity:>94%

Remarks: Acetone used as solvent. Water temperature, dissolved oxygen content, and pH monitored throughout study. Data reported at 95% confidence level.

Reference: Monsanto BN-76-254 EG&G Bionomics, 1976

Type of test: static **[X]**; semi-static **[]**; flow-through **[ ]**; other *(e.g. field test)* **[ ]** open-system **[ ]**; closed-system **[X]**

Species: Pimephales promelas (Fathead Minnows)

Exposure period: 96 hours

Results:
LC_{50} (24h) = 0.32 mg/l
LC_{50} (48h) = 0.28 mg/l
LC_{50} (72h) = Not Measured
LC_{50} (96h) = 0.28 mg/l
NOEC = Not Determined
LOEC = 0.10 mg/l

Analytical monitoring: Yes **[X]** No **[ ]** ? **[ ]**

Method: EPA Methods for Acute Toxicity Tests with Fish, Macroinvertebrates and Amphibians (1975)

GLP: Yes **[X]** No **[ ]** ? **[ ]** **Klimisch 1**

Test substance:. Santoflex 77 dark red liquid purity 99+%

Remarks: Acetone used as solvent. Water temperature, dissolved oxygen content, and pH monitored throughout study. Data reported at 95% confidence level. Quality check via Antimycin A challenge. Preliminary 72-hour range-finding study used to determine final concentrations.

Reference: Monsanto AB-79-1384361-1a, Analytical BioChemistry Labs, 1979

4.2 ACUTE TOXICITY TO AQUATIC INVERTEBRATES

*A. Daphnia

Type of test: static **[X]**; semi-static **[ ]**; flow-through **[ ]**; other *(e.g. field test)* **[ ]**; open-system **[ ]**; closed-system **[X]**

Species: Daphnia magna

Exposure period: 48 hours

Results: EC_{50} (24h) = 0.44 mg/l
EC_{50} (48h) = 0.37 mg/l
NOEC = 10 mg/l

Analytical monitoring: Yes **[X]** No **[ ]** ? **[ ]**

Method: EPA Methods for Acute Toxicity Tests with Fish, Macroinvertebrates and Amphibians (1975)

GLP: Yes **[X]** No **[ ]** ? **[ ]** **Klimisch 1**

Test substance: Santoflex 77 reddish-brown liquid, purity: 99+%

Remarks: Nanograde Acetone used to prepare stock solutions. Water quality parameters (temperature, dissolved oxygen, pH) monitored throughout study. Initial range-finding experiment used to select concentrations. Data reported at 95% confidence level.

Reference: Monsanto AB-79-1384361-1b Analytic Bio-Chemistry Labs, 1979

B. Other aquatic organisms

Type of test: static **[X]**; semi-static **[ ]**; flow-through **[ ]**; other *(e.g. field test)* **[ ]**; open-system **[ ]**; closed-system **[X]**

Species: Paratanytarsus parthenogenetica (Midge)

Exposure period: 48 hours

Results: EC_{50} (24h) = 4.4 mg/l
EC_{50} (48h) = 1.7 mg/l
NOEC = 0.56 mg/l

Analytical monitoring: Yes **[X]** No **[ ]** ? **[ ]**

Method: EPA Methods for Acute Toxicity Tests with Fish, Macroinvertebrates and Amphibians (1975)

GLP: Yes **[X]** No **[ ]** ? **[ ]** **Klimisch 1**

Test substance:. Santoflex 77 dark liquid, purity:>94%

Remarks: Stock solutions prepared in acetone. Range-finding experiment run to determine final experimental concentrations. Water quality parameters monitored throughout testing.

Reference: Monsanto AB-81-9AB981014, Analytical BioChemistry Labs, 1981

*4.3 TOXICITY TO AQUATIC PLANTS, e.g. algae

Species: Selenastrum capricornutum (Freshwater alga)

Endpoint: Biomass **[X]**; Growth rate **[ ]**; Other **[ ]**

Exposure period: 96 hours

Results: EC_{50} (24h) = >200 mg/l
EC_{50} (48h) = >120<200 mg/l

EC_{50} (72h) = 86 mg/l
EC_{50} (96h) = 52 mg/l
NOEC = Not Determined
LOEC = Not Determined

Analytical monitoring: Yes **[X]** No **[ ]** ? **[ ]**
Method: EPA Selenastrum capricornutum Algal Assay Test 1978
open-system **[ ]**; closed-system **[X]**
GLP: Yes **[X]** No **[ ]** ? **[ ]** **Klimisch 1**
Test substance: Santoflex 77 blackish-red liquid, Lot# KL01-04, purity: 99+%
Remarks: Stock solutions prepared in DMSO. Both cell numbers and decrease of in vivo chlorophyll a measured. Triplicate cultures employed for all test concentrations and for controls. pH monitored throughout test.
Reference: Monsanto BN-79-1384361-2, EG&G Bionomics, 1979

4.5 CHRONIC TOXICITY TO AQUATIC ORGANISMS

4.5.1 CHRONIC TOXICITY TO FISH (*effects on reproduction, embryo/larva, etc.*)

Type of test: static **[ ]**; semi-static **[ ]**; flow-through **[X]**; other *(e.g. field test)* **[]**; open-system **[ ]**; closed-system **[x]**
Species: Pimephales promelas (Fathead Minnow)
Endpoint: Length of fish **[ ]**; Weight of fish **[X]**;
Reproduction rate **[ ]**; Other **[ ]**
Exposure period: 14 days
Results: EC_{50} (14d) = 0.067 mg/l
NOEC = 0.018 mg/l
LOEC = 0.046 mg/l
Analytical monitoring: Yes **[X]** No **[ ]** ? **[ ]**
Method: EPA Methods for Acute Toxicity Tests with Fish, Macroinvertebrates and Amphibians (1975) and Committee on Methods for Toxicity Tests with Aquatic Organisms, 1975
GLP: Yes **[X]** No **[ ]** ? **[ ]** **Klimisch 1**
Test substance: Santoflex 77 dark liquid, purity: 99+%
Remarks: Stock solutions prepared in Methanol. Water quality parameters monitored throughout test and remained withing acceptable limits. Behavior observations throughout the test indicated that mortality was preceded by surfacing and loss of equilibrium. Weight measurements of surviving fish at the end of the study yielded the following weight percentages of the control group mean weight: 0.018 mg/l = 84%, and 0.046 mg/l = 81%. An apparent lethal threshold of the test substance to fathead minnows was determined to be 0.067 mg/l and was reached after 12 days as indicated by a cessation in mortality from days 12-14.
Reference: Monsanto AB-80-1803058-B1, Analytical BioChemistry Labs, 1981

Type of test: static **[ ]**; semi-static **[ ]**; flow-through **[X]**; other *(e.g. field test)* **[]**; open-system **[ ]**; closed-system **[x]**
Species: Pimephales promelas (Fathead Minnow)
Endpoint: Length of fish **[X]**; Weight of fish **[X]**;
Reproduction rate **[ ]**; Other **[ ]**
Exposure period: 14 days (336 hours)
Results: LC_{50} (24h) = 0.07 mg/l

LC_{50} (96h) = 0.06 mg/l
LC_{50} (14d) = 0.05 mg/l
NOEC = Not Determined
LOEC = Not Determined

Analytical monitoring: Yes **[X]** No **[ ]** ? **[ ]**

Method: EPA Methods for Acute Toxicity Tests with Fish, Macroinvertebrates and Amphibians (1975) and Committee on Methods for Toxicity Tests with Aquatic Organisms, 1975

GLP: Yes **[X]** No **[ ]** ? **[ ]** **Klimisch 1**

Test substance: Santoflex 77 dark reddish liquid, purity: 99+%

Remarks: Stock solutions prepared in acetone and stabilized with ascorbic acid. Water quality parameters monitored throughout test and remained withing acceptable limits. Samples analyzed for concentration of test article varied widely. This variability was attributed to the instability of the test compound in water and to incomplete dispersion. Nominal concentrations of test compound were 0.00, 0.03, 0.06, 0.12, 0.25 and 0.50 mg/l. LC50s were recorded at 24, 96 and 336 hours. At the time the test was terminated, no mortalities had occurred during the preceeding 48 hours.

Reference: Monsanto SR-80-1803058-A1, SRI International, 1981

5. TOXICITY

*5.1 ACUTE TOXICITY

5.1.1 ACUTE ORAL TOXICITY

Type: LD_0 **[ ]**; LD_{100} **[ ]**; LD_{50} **[X]**; LDL_0 **[ ]**; Other **[ ]**

Species/strain: Sprague-Dawley Albino Rats

Value: 730 mg/kg b.w.
Discriminating dose: 794 mg/kg

Method: Defined Lethal Dose

GLP: Yes **[ ]** No **[ ]** ? **[x]** **Klimisch 2**

Test substance: Santoflex 77, Lot # KC01-04 , purity:>94%

Remarks: Groups of male and female rats were fed either 501, 631, 704 or 1000 mg/kg of the undiluted test substance as a single oral dose by gavage. Clinical signs of toxicity included reduced appetite and activity – for to six days in survivors – followed by increasing weakness, collapse and death. Gross autopsy findings on decedents included hemorrhagic areas of the lungs, liver discoloration and acute gastrointestinal inflammation. Survivors were sacrificed after 10 days. All viscera examined appeared normal.

Reference: Monsanto Y-73-168 Younger Laboratories, 1973

5.1.2 ACUTE INHALATION TOXICITY

Type: LC_0 **[X]**; LC_{100} **[ ]**; LC_{50} **[ ]**; LCL_0 **[ ]**; Other **[ ]**

Species/strain: Sprague-Dawley Albino rats

Exposure time: 6 hours w/10 day observation period

Value: Sample did not vaporize

Method: Ambient Temperature Inhalation

GLP: Yes **[ ]** No **[ ]** ? **[x]** **Klimisch 2**

Test substance: Santoflex 77 Lot # KC01-04, purity: >94%

Remarks: Male rats were exposed to the test article in an inhalation chamber for a period of six hours at ambient temperature. The initial sample size of the test article was 133 grams. At the end of six hours, the sample was reweighed and found to be 133 grams, and no sample was recovered from the chamber air condenser. Santoflex 77 did not vaporize under the test conditions. No animal experienced any symptoms of toxicity. The 10 day observation period was uneventful, and all animals survived to sacrifice with no noted ill-effects. Autopsy findings were that all viscera examined appeared normal.

Reference: Monsanto Y-73-168 Younger Laboratories, 1973

5.1.3 ACUTE DERMAL TOXICITY

Type: LD_0 **[ ]**; LD_{100} **[ ]**; LD_{50} **[X]**; LDL_0 **[ ]**; Other **[ ]**

Species/strain: New Zealand Albino Rabbits

Value: >3160 mg/kg b.w.

Method: Defined Lethal Dose

GLP: Yes **[ ]** No **[ ]** ? **[X]** **Klimisch 2**

Test substance: Santoflex 77, Lot # KC01-04, purity: >94%

Remarks: The undiluted test substance was applied to the shaved skin of male and female rabbits for a period of 24 hours, followed by a 14 day recovery period. Dosages were 1260, 2000, 3160, 5010 or 7940 mg/kg. Clinical signs of toxicity were reduced appetite and activity – three to seven days in survivors – followed by increasing weakness, collapse and death. Gross autopsy findings on decedents included lung hyperemia, liver discoloration, enlarged gall bladder and gastrointestinal inflammation. Survivors were sacrificed following the recovery period. All viscera appeared normal on all but two animals, which exhibited a slight discoloration of both liver and kidneys.

Reference: Monsanto Y-73-168 Younger Laboratories, 1973

5.2 CORROSIVENESS/IRRITATION

5.2.1 SKIN IRRITATION/CORROSION

Species/strain: New Zealand Albino Rabbits

Results: Highly corrosive **[ ]**; Corrosive **[ ]**; Highly irritating **[ ]**; Irritating **[ ]**; Moderate irritating **[ ]**; Slightly irritating **[ ]**; Not irritating **[X]**

Classification: Highly corrosive (causes severe burns) **[ ]**; Corrosive (causes burns) **[ ]**; Irritating **[ ]**; Not irritating **[X]**

Method: Primary Skin Irritation

GLP: Yes **[ ]** No **[ ]** ? **[X]** **Klimisch 2**

Test substance: Santoflex 77 Lot #KC01-04, purity:>94%

Remarks: 0.5 ml of the undiluted test substance was applied to the shaved skin of six male and female rabbits. Irritation was scored on a scale of 0-4 for both erythema and edema. The 24 hour score for all animals was 0.0, indicating the the test substance was non-irritating. Observations noted was a slight defatting effect on the skin, with mild flaking after 7-10 days.

Reference: Monsanto Y-73-168 Younger Laboratories, 1973

5.2.2 EYE IRRITATION/CORROSION

Species/strain: New Zealand Albino Rabbits

Results Highly corrosive **[ ]**; Corrosive **[ ]**; Highly irritating **[ ]**;

Irritating **[ ]**; Moderate irritating **[ ]**; Slightly irritating **[X]**;
Not irritating **[ ]**

Classification: Irritating **[X]**; Not irritating **[ ]**; Risk of serious damage to eyes **[ ]**

Method: Draize

GLP: Yes **[ ]** No **[ ]** ? **[X]** **Klimisch 2**

Test substance: Santoflex 77 Lot # KC01-04, purity: >94%

Remarks: 0.1 ml of the undiluted test substance was applied to the eyes of rabbits. Irritation was assessed at 1, 24, 48, 72 and 168-hour intervals on the basis of irritation to the cornea, iris and conjunctivae. Immediate findings were slight discomfort. 1-hour findings were slight erythema, very slight edema and copious discharge. 24-hour score was 10.0, 48-hour score was 9.3, 72-hour score was 6.3 and 168-hour score was 0.0. The 24/48/72 hour average score was 8.5 for a classification as a "slight" acute eye irritant.

Reference: Monsanto Y-73-168 Younger Laboratories, 1973

5.3 SKIN SENSITISATION

Type:

Species/strain:

Results: Sensitizing **[ ]**; Not sensitizing **[ ]**; Ambiguous **[ ]**

Classification: *(if possible, according to EC Directive 67/548/EEC)*
Sensitizing **[ ]**; Not sensitizing **[ ]**

Method:

GLP: Yes **[ ]** No **[ ]** ? **[ ]**

Test substance: . . . . . , purity: . . . . . .

Remarks:

Reference:

*5.4 REPEATED DOSE TOXICITY

Species/strain: Sprague-Dawley CD Rats

Sex: Female **[ ]**; Male **[ ]**; Male/Female **[X]**; No data **[ ]**

Route of Administration: Oral/Dietary

Exposure period: 30 days

Frequency of treatment: Daily

Post exposure observation period:

Dose: 0, 100, 300, 500, 1000 and 2000 ppm

Control group: Yes **[X]**; No **[ ]**; No data **[ ]**;
Concurrent no treatment **[X]**; Concurrent vehicle **[ ]**; Historical **[ ]**

NOEL: 100 ppm for males, 300 ppm for females

LOEL: Not Determined

Results: In a 30-day range-finding study that preceeded a 90-day study, the test substance was administered orally, via dietary admixture, to groups of male and female rats (5/sex/group). Control animals received the standard laboratory diet. Physical observations, body weight and food consumption measurements were performed on all animals pretest and at selected intervals during the study. Hematology and chemistry determinations were performed on all animals at study termination. There were no mortalities during the course of the study. After four weeks of treatment, all animals were sacrificed, selected organs were weighed, and organ/body weight ratios were calculated. Complete postmortem examinations were conducted on all animals. Differences from control in mean body weights were statistically significant at 500 ppm and 1000 ppm males and in 2000

ppm males and females. Differences from control in mean body weight/body weight gain suggested a treatment-related effect in males at dose levels at and above 300 ppm, and in females at and above 1000 ppm. Food consumption values in Week 1 were reduced for males at 500 ppm and above, and for females at 300 ppm and above. Food consumption at Weeks 3-4 was comparable to controls. Males and females at the two highest dose levels exhibited increased mean platelet counts following four weeks of treatment. Males in these groups also exhibited increased mean erythrocyte. The mean hematology values for males and females in all treatment groups were comparable to controls. Alterations in several clinical chemistry parameters were noted for higher dose levels. Mean terminal body weights were reduced at the two highest dose levels in females, and at the three highest dose levels in males. While several organs in treated males and females exhibited alterations in either mean absolute or relative weights, these changes were considered secondary effects and not indicative of significant organ toxicity. Gross pathological examination did not reveal any effects that were considered treatment-related.

Method: Dunnett, C.W., A Multiple Comparison Procedure for Comparing Several Treatments with a Control, Jour. Am. Stat. Assoc. 50: 1096-1121, 1955

GLP: Yes **[X]** No **[ ]** ? **[ ]** **Klimisch 1**

Test substance:. Santoflex 77 Lot# KJ01-03, purity: 99+% active

Reference: Monsanto BD-87-146 Bio/dynamics Labs, 1987

Species/strain: Sprague-Dawley CD Rats

Sex: Female **[ ]**; Male **[ ]**; Male/Female **[X]**; No data **[ ]**

Route of Administration: Oral/Dietary

Exposure period: 90 days

Frequency of treatment: Daily

Post exposure observation period:

Dose: Males: 0, 100, 250 and 500 ppm Females: 0, 250, 500 and 750 ppm

Control group: Yes **[X]**; No **[ ]**; No data **[ ]**;
Concurrent no treatment **[X]**; Concurrent vehicle **[ ]**; Historical **[ ]**

NOEL: 100 ppm for males, not established for females

LOEL: Not Determined

Results: The test substance was administered orally, via dietary admixture, to groups of male and female rats (10/sex/group). Control animals received the standard laboratory diet. Physical observations, body weight and food consumption measurements were performed on all animals pretest and at selected intervals during the study. Hematology and chemistry determinations were performed on all animals at Months 1.5 and 3. There were no mortalities during the course of the study. After three months of treatment, all animals were sacrificed, selected organs were weighed, and organ/body and organ/brain weight ratios were calculated. Complete postmortem examinations were conducted on all animals. Histopathological evaluation of selected tissues was performed on all control and high-dose animals. The lungs, spleen, liver and kidneys were examined microscopically for all animals in all groups. Mean body weights and mean body weight gains were reduced in males at 250 and 500 ppm,

and in all treated females. Overall, mean food consumption values for all treated groups were comparable to controls. Several clinical chemistry parameters exhibited statistically significant differences from control. Alkaline phosphatase was elevated in the 500 ppm males and 750 ppm females at Month 3. Mean serum glutamic oxaloacetic transaminase levels were significantly reduced in the 100, 250 and 500 ppm males at Month 1.5 but not at Month 3. Mean serum glutamic pyruvic transaminase was reduced in the 500 and 750 ppm females at Month 3. Several organs in the treated males and females exhibited alterations in mean absolute and/or relative (to body or brain) weight data. However, these alterations were generally consistent with the reductions noted in body weight data and were considered secondary effects which were not considered indicative of significant organ toxicity. There were no treatment-related findings noted in mortality, physical observations, opthalmoscopic, hematology, organ weight or gross and microscopic pathology.

Method: OECD Guidelines for Testing of Chemicals, Section 453, 1981 and USEPA TSCA Section 4(a) Test Rules, 1982

GLP: Yes **[X]** No **[ ]** ? **[ ]** **Klimisch 1**

Test substance:. Santoflex 77 Lot# KJ01-03, purity: 99+% active

Reference: Monsanto BD-87-147 Bio/dynamics Labs, 1989

Species/strain: Charles River Albino rats

Sex: Female **[ ]**; Male **[ ]**; Male/Female **[X]**; No data **[ ]**

Route of Administration: Oral/Dietary

Exposure period: 2 years

Frequency of treatment: Daily

Post exposure observation period:

Dose: 0, 30, 100 or 300 ppm

Control group: Yes **[X]**; No **[ ]**; No data **[ ]**;
Concurrent no treatment **[X]**; Concurrent vehicle **[ ]**; Historical **[ ]**

NOEL: 30 ppm

LOEL: 100 ppm

Results: A two-year chronic oral toxicity study was conducted on groups of 400 CD Outbred rats (50/sex/dose) at dietary levels ranging from 0-300 ppm. Reductions in body weights and body weight gains were noted for males and females at the 300 ppm dose throughout the investigation. Body weights of females fed 100 ppm were reduced during the first 7 weeks, and for 100 ppm males for the first 4 weeks. After those intervals, body weights compared favorably with controls. 30 ppm animals had body weights and weight gains that compared favorably with controls. Frequency and distribution of deaths during the investigation for all dose levels was similar to controls. Gross pathological examination of animals that died during the study did not reveal any relation between death and exposure to the test substance. No unusual behavioral reactions were noted in dosed animals during the course of the study. Results of hematologic studies conducted – total and differential leukocyte count, erythrocyte count, hemoglobin concentration, hematocrit value, mean corpuscular volume, mean corpuscular hemoglobin and mean corpuscular hemoglobin concentration – were either similar to, or within the range of expected values for this strain of albino rats of this age and in this laboratory. Results of clinical blood chemistry studies (SGPT, BUN, SGOT, Fasting

Blood Glucose Concentration, SAP) and of urinalyses (glucose, albumin, microscopic elements, pH and specific gravity) conducted showed similar results between control and test animals. Gross pathological examinations of animals sacrificed at 24 months revealed similar findings between test and control animals. Histopathological examinations of tissues and organs from the control and 300 ppm animals sacrificed at 24 months showed no treatment-related lesions. Microscopic examination of suspect neoplasms among all sacrificed animals and all animals that died during the study were conducted. No differences were noted between test and control rats as to the organ system involved, the type or the classification of neoplasms. The spectrum of neoplasms observed compared favorably to historical data at this laboratory for rats of this strain and age. At 17.5 months of testing, tetracycline HCl was added to the diets of all groups (30g/kg of diet) for a two-week period to treat a severe respiratory infection which caused an increase in mortality in both control and treated animals.

Method: 2-Year Chronic Oral Toxicity IBT Protocol # 622-05400B (1974)
GLP: Yes **[X]** No **[ ]** ? **[ ]** **Klimisch 1**
Test substance: Santoflex 77 reddish liquid Lot# KD05-57, purity: 99+% active
Reference: Monsanto BTL-74-27, Industrial Bio-Test Labs, 1978

*5.5 GENETIC TOXICITY IN VITRO

A. BACTERIAL TEST

Type: Ames Reverse Bacterial Mutation
System of testing: Salmonella typhimurium TA98, TA100, TA1535, TA1537
Concentration: 0.01, 0.04, 0.2, 1, 3, 10, 40 and 200 micrograms/plate
Metabolic activation: With **[ ]**; Without **[ ]**; With and Without **[X]**; No data **[ ]**
Results:
Cytotoxicity conc: With metabolic activation: 200 micrograms/plate
Without metabolic activation: 10 micrograms/plate
Precipitation conc: 1 microgram/plate
Genotoxic effects:

	+	?	-
With metabolic activation:	**[ ]**	**[ ]**	**[X]**
Without metabolic activation:	**[ ]**	**[ ]**	**[X]**

Method: Ames, B.N., McCann, J. and Yamaski, E. Methods for Detecting Carcinogens and Mutagens with the Salmonella Mammalian-Microsome Test. Mutat. Res. 31, 347-364, 1975
GLP: Yes **[X]** No **[ ]** ? **[ ]** **Klimisch 1**
Test substance: Santoflex 77 Lot# 7/31/85WGK, purity: 99+% active
Remarks: Santoflex 77 was tested in Ames/Salmonella plate incorporation assays using the tester strains TA98, TA100, TA1535 and TA1537 in the presence and absence of an Aroclor-induced rat liver mammalian metabolic activation system (S-9 Mix). No mutagenic activity was observed for the test compound in any of these assays. Toxicity of the test compound was significantly reduced in the presence of the S-9 Mix.
Reference: Monsanto ML-85-242 Environmental Health , 1985

B. NON-BACTERIAL IN VITRO TEST

Type:	Mammalian Cell Gene Forward Mutation Assay
System of testing:	L5178Y Mouse Lymphoma cells
Concentration:	0.002, 0.004, 0.008, 0.016 (without activation) 0.002, 0.004, 0.008, 0.016, 0.032 (with activation)
Metabolic activation:	With **[ ]**; Without **[ ]**; With and Without **[X]**; No data **[ ]**
Results:	
Cytotoxicity conc:	With metabolic activation: 0.032 ug/ml Without metabolic activation: 0.016 ug/ml
Precipitation conc:	Not determined
Genotoxic effects:	+ ? - With metabolic activation: **[ ] [ ] [X]** Without metabolic activation: **[ ] [ ] [X]**
Method:	Clive and Spector, Mutation Research 31:17-29 (1975)
GLP:	Yes **[ ]** No **[ ]** ? **[X]** **Klimisch 2**
Test substance:	CP-25477 (Santoflex 77) dark liquid, purity >94%
Remarks:	The test article was evaluated for specific locus forward mutation in the L5178Y Thymidine Kinase (TK) mouse lymphoma cell assay. Stock solutions were prepared in DMSO. DMSO was used as the negative control. EMS was used as the positive control without activation and DMN was used as the positive control with activation. The test article was found to be negative
Reference:	Monsanto BIO-76-246 Litton Bionetics, 1976

Type:	*In vitro* Unscheduled DNA Synthesis (UDS)
System of testing:	Primary rat hepatocyte cultures (Fischer-344 strain)
Concentration:	0.01, 0.05, 0.1, 0.5, 1, 5, 10, 20, 50, 100, 500, 1000 ug/ml
Metabolic activation:	With **[ ]**; Without **[ ]**; With and Without **[X]**; No data **[ ]**
Results:	
Cytotoxicity conc:	Preliminary Assay: 50 ug/ml Replicate Assay: 5 ug/ml
Precipitation conc:	Separation (two layers) at 1000 ug/ml
Genotoxic effects:	+ ? - **[ ] [ ] [X]**
Method:	Williams, G.M., Detection of Chemical Carcinogens by Unscheduled DNA Synthesis in Rat Liver Primary Cell Cultures, Cancer Research 37, pp. 1845-1851 (1977)
GLP:	Yes **[X]** No **[ ]** ? **[ ]** **Klimisch 1**
Test substance:	Santoflex 77 liquid produced 07/31/85, purity 99+% active
Remarks:	Acetone (1%) used as solvent and diluent. Primary rat liver cell cultures derived from the livers of two adult male rats. The positive control was 2-AAF, the solvent control was acetone in the preliminary assay and DMSO in the replicate assay. The percentage of cells in repair was calculated as the percentage of cells with at least 5 net grains/nucleus. 150 cells were scored for each concentration reported for each experiment. The net grain counts were negative at each concentration of the test compound, in the solvent control and in the medium control, in contrast to the strong positive response produced by the positive control 2-AAF in both experiments. These results indicate that Santoflex 77 is not a genotoxic agent under the conditions of the in vitro rat hepatocyte DNA repair assay.
Reference:	Monsanto SR-85-250, SRI International, 1986

*** 5.6 GENETIC TOXICITY IN VIVO**

Type:
Species/strain:
Sex: Female **[ ]**; Male **[ ]**; Male/Female **[ ]**; No data **[ ]**
Route of Administration:
Exposure period:
Doses:
Results:
Effect on mitotic
index or P/N ratio:
Genotoxic effects: + ? -
[ ] [ ] [ ]
Method:
GLP: Yes **[ ]** No **[ ]** ? **[ ]**
Test substance:
Remarks:
Reference:

5.7 CARCINOGENICITY

Species/strain:
Sex: Female **[ ]**; Male **[ ]**; Male/Female **[ ]**; No data **[ ]**
Route of Administration:
Exposure period:
Frequency of treatment:
Postexposure observation period:
Doses:
Control group: Yes **[ ]**; No **[ ]**; No data **[ ]**;
Concurrent no treatment **[ ]**; Concurrent vehicle **[ ]**; Historical **[ ]**
Results:
Method:
GLP: Yes **[ ]** No **[ ]** ? **[ ]**
Test substance:` . . . . . , purity: . . . . . .
Remarks:
Reference:

***5.8 TOXICITY TO REPRODUCTION**

Type: Fertility **[X]**; One-generation study **[ ]**; Two-generation study **[ ]**;
Other **[X]** Three Generation Study
Species/strain: Charles River Albino Rats
Sex: Female **[ ]**; Male **[ ]**; Male/Female **[X]**; No data **[ ]**
Route of Administration: Oral/Dietary
Exposure period: Premating, throughout mating, gestation and lactation
Frequency of treatment: Daily
Post exposure observation period: Not Determined
Premating exposure period: male: F0 – 14 wks F1- 14 wks F2 – 18 wks
female: F0 – 14 wks F1 – 14 wks F2 – 18 wks
Duration of the test: F0 – 23 wks F1 – 23 wks F2 – 26 wks
Doses: 0, 30, 100 or 300 ppm
Control group: Yes **[X]**; No **[ ]**; No data **[ ]**;
Concurrent no treatment **[X]**; Concurrent vehicle **[ ]**; Historical **[ ]**
NOEL Parental: 30 ppm (based on reduced body weight gain)

NOEL F1 Offspring: 30 ppm (based on reduced pup survival)
NOEL F2 Offspring: 30 ppm (based on reduced pup survival)
Results: Santoflex 77 was administered to three successive generations of rats at dose levels of 0, 30, 100 or 300 ppm. Dose levels were selected on the basis of results from a previous 2-year chronic oral feeding study. No adverse effects on mating or fertility indices were noted in any of the treated animals. Reduced survival of offspring was observed in the mid- to high-dose groups. Evidence of parental toxicity was also present as indicated by reduced body weights of mid-to high-dose animals

General parental toxicity: Reduced body weights and mean body weight gains were noted for the 100 and 300 ppm males and females. No other treatment-related effects were evident in results of clinical blood chemistry studies and urinalyses between the control groups and the treated animals.

Toxicity to offspring: A small but statistically significant reduction in the survival rates of pups was noted in the 100 ppm and 300 ppm groups.

Method: 3-Generation Reproductive Toxicity IBT Protocol # 622-05400C (1974)
GLP: Yes **[ ]** No **[ ]** ? **[X]** **Klimisch 2**
Test substance: Santoflex 77 dark red liquid Lot# KD05-57, purity: 99+% active
Remarks: Protocol similar to Monsanto BTL-74-27, Industrial Bio-Test Labs, 1978
Reference: Monsanto BTL-76-145, Industrial Bio-Test Labs, 1976

***5.9 DEVELOPMENTAL TOXICITY/ TERATOGENICITY**

Species/strain: Charles River CD Albino Rats
Sex: Female **[X]**; Male **[ ]**; Male/Female **[ ]**; No data **[ ]**
Route of Administration: Oral gavage
Duration of the test: 25 days from mating to last C-section
Exposure period: Day 6-15 of gestation
Frequency of treatment: Daily, as a single oral dose at a volume of 5 ml/kg
Doses: 25, 75 and 150 mg/kg/day
Control group: Yes **[X]**; No **[ ]**; No data **[ ]**;
Concurrent no treatment **[ ]**; Concurrent vehicle **[X]**; Historical **[ ]**
NOEL Maternal Toxicity: 25 mg/kg/day
NOEL teratogenicity : 150 mg/kg/day
Results: Groups of 25 mated CD rats were assigned to one control group and three treatment groups to determine the teratogenic potential of the test substance. Dosage levels of 25, 75 and 150 mg/kg/day were administered orally by gavage as a single daily dose on Days 6-15 of gestation. The control group received the corn oil vehicle only. Cesarean sections were performed on all surviving females on gestation Day 20, and the fetuses removed for teratologic evaluation.

Maternal general toxicity: Toxicity in the dams was apparent at the 75 and 150 mg/kg/day dosage levels. Parameters adversely affected were maternal survival, appearance, behavior and body weight gain. Four of the 150 mg/kg/day females and one 75 mg/kg/day female died between gestation Days 16-17. Control animals and the low dose group had 100% survival. Antemortem abnormalities in the decedents included dried blood around and/or expelled from the vaginal orifice, blood under the cage, stained, wet or matted coat, hypothermia and ptyalism. There were no treatment-related gross internal lesions evident. No effect on Cesarean section observations was noted in the dams at any dosage level.

Pregnancy/litter data: No obvious differences were noted between the

Treated groups and the control group.
Foetal data: Malformations that were observed in the treated groups occurred in low incidence and were not considered treatment-related. One high-dose fetus had anophthalmia, one mid-dose and two control group fetuses had microphthalmia, and another mid-dose fetus had ectopia cordia and sternoschisis. There were no adverse effects on the fetal parameters examined (survival, growth, morphological development) at dose levels at or below 150 mg/kg/day.

Method: OECD Guidelines for Testing of Chemicals No. 414 "Teratogenicity" 1981, and TSCA Health Effects Guidelines "Teratogenicity Study" 1982

GLP: Yes **[X]** No **[ ]** ? **[ ]** **Klimisch 1**

Test substance: Santoflex 77 red-brown liquid Lot# 25477, purity: 99+% active

Remarks: Based on the results, the test article did not induce developmental toxicity In the offspring of Charles Rived CD rats under the test conditions.

Reference: Monsanto IR-85-290 International Research and Development, 1986

5.10 OTHER RELEVANT INFORMATION

A. Specific toxicities

Type: Immunotoxicity – Repeated Insult Patch Testing
Modified Schwartz Method and Shelanski Method

Results: Several studies were run using human volunteers to determine the potential for Santoflex 77 to cause allergic skin reactions in compounded rubber stocks. Loading of the test article was from 0.5 to 3 phr (parts per hundred rubber) in a typical B-1 Masterbatch. Some study results indicated that the test article caused no primary irritation and no allergic response, while other study results were positive for sensitization.

Remarks: Differences in responses may be due to the presence of other chemicals in the B-1 masterbatch formulations.

Reference: Monsanto SH-61-17, Industrial Biology Labs, 1961
Monsanto SH-63-10, Industrial Biology Labs, 1963
Monsanto SH-64-4, Industrial Biology Labs, 1964
Monsanto SH-64-5, Industrial Biology Labs, 1964
Monsanto SH-73-12, Industrial Biology Labs, 1973

B. Toxicodynamics, toxicokinetics

Type: *(e.g. toxicodynamics, toxicokinetics)*
Results:
Remarks:
References:

*** 5.11 EXPERIENCE WITH HUMAN EXPOSURE**

Results:
Remarks:
Reference:

6. REFERENCES

1. United States National Toxicology Program, November 6, 1990
2. Monsanto Physical Constants of CP25447. Standard Manufacturing Process Manual, July 1977
3. American Society for Testing and Materials, 1997
4. Monsanto SRI 8669, Selected Environmental Fate Studies of Nine Chemical Compounds, SRI International, August 20, 1980

5. USEPA federal Register Volume 44, No. 53, March 16, 1979, pp. 16 and 255
6. American Society for Testing and Materials, D 92, Standard Test Method for Flash and Fire Points by Cleveland Open Cup, 1997
7. Monsanto Report ABC-32303, Santoflex 77 Phase I Hydrolysis Study: Identification of Hydrolysis Products, Analytical BioChemistry Laboratories, January 15, 1986
8. Monsanto ES-79-SS-25, Environmental Persistence Screening of Selected Rubber Chemicals, Monsanto Industrial Chemicals Environmental Sciences, December 28, 1979
9. American Society for Testing and Materials, Draft Method No. 2, ASTM Committee E35.24, August 1979
10. Monsanto BN-76-254 Acute (96 Hour) Toxicity of Santoflex 77 to Rainbow Trout, EG&G Bionomics Aquatic Toxicity Laboratory, December 1976
11. Monsanto BN-76-254 Acute (96 Hour) Toxicity of Santoflex 77 to Bluegill Sunfish, EG&G Bionomics Aquatic Toxicity laboratory, December 1976
12. Monsanto AB-79-1384361-1b Acute Toxicity of Santoflex 77 to Daphnia magna, Analytical BioChemistry Laboratories, August 27, 1979
13. Monsanto AB-79-1384361-1a Acute Toxicity of Santoflex 77 to Fathead Minnows, Analytical BioChemistry Laboratories, August 27, 1979
14. Monsanto BN-79-1384361-2 Toxicity of Santoflex 77 to the freshwater alga Selenastrum capricornutum, EG&G Bionomics Marine Research Laboratory, August 1979
15. Monsanto AB-81-9AB981014, Acute Toxicity of Santoflex 77 to Midge, Analytical BioChemistry Laboratories, August 19, 1981
16. Gettings, A.V and W.J. Adams. 1980. Method for Conducting Acute Toxicity Tests with the Midge Paratanytarsus parthenogenetica. Monsanto Industrial Chemicals Company, Report ES-81-M-1
17. C.E. Stephan, Chairman, Committee on Methods for Toxicity Tests with Aquatic Organisms, US EPA, 1975
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19. Monsanto SR-80-1803085-A1, Time Independent Toxicity Study on Santoflex 77 using Fathead Minnows as the Test Organism, SRI International, September 8, 1981
20. Monsanto Y-73-168, Toxicological Examination of CP-25477 (Santoflex 77) for Acute Oral and Dermal Toxicity, Younger Laboratories, October 9, 1973
21. Monsanto Y-73-168, Toxicological Examination of CP-25477 (Santoflex 77) for Ambient Temperature Inhalation Toxicity, Younger Laboratories, October 9, 1973
22. Monsanto Y-73-168, Toxicological Examination of CP-25477 (Santoflex 77) for Acute Eye and Primary Skin Irritation, Younger Laboratories, October 9, 1973
23. Monsanto BD-87-146, A 4 Week Range-Finding Toxicity Study with Santoflex 77 in the Rat Via Dietary Admixture, Bio/dynamics, Inc. June 14, 1989
24. Monsanto BD-87-147, A Subchronic 3-Month Oral Toxicity Study with Santoflex 77 in the Rat Via Dietary Admixture, Bio/dynamics, Inc. April 28, 1989
25. Monsanto BTL-74-27, Two-Year Chronic Oral Toxicity Study with Santoflex 77 in Albino Rats, Industrial Bio-Test Laboratories, Inc. November 27, 1978
26. Monsanto ML-85-242, Ames/Salmonella Mutagenicity Assay of Santoflex 77, Monsanto Environmental Health Laboratory, February 18, 1986
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28. OECD Guidelines for Testing of Chemicals: No. 414, Teratogenicity, adopted May 1981
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30. Monsanto IR-85-290, Teratology Study in Rats with Santoflex 77, International Research and Development Corporation, April 1, 1986

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32. Monsanto SH-63-10, Modified Schwartz Patch Test Study of Monsanto Rubber Samples, Industrial Biology Laboratories, Inc., November 8, 1963

33. Monsanto SH-64-4, Repeat Insult Patch Test on Vulcanized Rubbers, Industrial Biology Laboratories, May 5, 1964

34. Monsanto SH-64-5, Dermatitic Studies of Hexyl- and Heptyl-PPDs in Rubber, Industrial Biology Laboratories, March 1964

35. Monsanto SH-73-12, Repeat Insult Patch Test with Uncured Rubbers, Industrial Biology Laboratories, April 1973

3081-01-4
p-Phenylenediamine, N-(1,4-dimethylpentyl)-N'-phenyl-

2. PHYSICAL-CHEMICAL DATA

*2.1 MELTING POINT

Value:	32.4°C for highly purified (99+%) Otherwise, room temperature viscous liquid
Decomposition:	Yes **[ ]** No **[X]** Ambiguous **[ ]**
Sublimation:	Yes **[ ]** No **[X]** Ambiguous **[ ]**
Method:	Crystallizing Point
GLP:	Yes **[ ]** No **[ ]** ? **[X]** **Klimisch 2**
Remarks:	Physical Constants, Flexsys SMP, R.L. Wright (1982)
Reference:	Flexsys 7PPD Standard Manufacturing Process

*2.2 BOILING POINT

Value:	231 °C
Pressure:	at 3.5 mm Hg
Decomposition:	Yes **[ ]** No **[X]** Ambiguous **[ ]**
Method:	Instrumental – Differential Scanning Calorimeter (DSC)
GLP:	Yes **[X]** No **[ ]** ? **[ ]** **Klimisch 1**
Remarks:	Physical Constants, Flexsys SMP, R.L. Wright (1982)
Reference:	L.M. Baclawski Notebook #2355311 (1982)

†2.3 DENSITY (relative density)

Type:	Bulk density **[ ]**; Density **[X]**; Relative Density **[ ]**
Value:	1.0
Temperature:	20 °C
Method:	Flexsys Standard Method of Analysis FF97.4-1
GLP:	Yes **[X]** No **[ ]** ? **[ ]**
Remarks:	Hydrometer method. Hydrometer must meet standards set in ASTM-E-100
Reference:	Flexsys 7PPD Standard Manufacturing Specifications

*2.4 VAPOUR PRESSURE

Value:	1.25 x 10(-10) mm Hg
Temperature:	25 °C
Method:	calculated **[X]**; measured **[ ]** Antoine Equasion.
GLP:	Yes **[ ]** No **[X]** ? **[ ]** **Klimisch 2**
Remarks:	None
Reference:	Monsanto Toxicology Profile, Santoflex 14, C.E. Healy 1993

*2.5 PARTITION COEFFICIENT $\log_{10}P_{ow}$

Log Pow:	5.17
Temperature:	Not Applicable
Method:	calculated **[X]**; measured **[ ]** **Klimisch 2** . SRC LogKow (KowWin) Program 1995
GLP:	Yes **[ ]** No **[X]** ? **[ ]**
Remarks:	None

Reference: Meylan, W.M. and. P.H. Howard, 1995 J. Pharm. Sci. 84: 83-92

*2.6 WATER SOLUBILITY

A. Solubility

Value: 0.67 mg/l in pH 7.0 deionized water
Temperature: 25°C
Description: Miscible **[ ]**; Of very high solubility **[ ]**;
Of high solubility **[ ]**; Soluble **[ ]**; Slightly soluble **[ ]**;
Of low solubility **[ ]**; Of very low solubility **[X]**; Not soluble **[]**
Method: Saturated Solution/GC Analysis
GLP: Yes **[X]** No **[]** ? **[ ]** **Klimisch 1**
Remarks: Preliminary solubility study for Phase I Hydrolysis
Reference: Monsanto ABC 32305, Analytical Bio-Chemistry Labs, 1986

B. pH Value, pKa Value

pH Value: Not Applicable
Concentration:
Temperature:
Method: .
GLP: Yes **[ ]** No **[ ]** ? **[ ]**
pKa value
Remarks:
Reference:

2.11 OXIDISING PROPERTIES

Results: Maximum burning rate equal or higher than reference mixture **[ ]**;
Vigorous reaction in preliminary test **[ ]**;
No oxidising properties **[X]**; Other **[ ]**
Method:
GLP: Yes **[ ]** No **[ ]** ? **[ ]**
Remarks:
Reference:

†2.12 OXIDATION: REDUCTION POTENTIAL

Value: Not Applicable
Method:
GLP: Yes **[ ]** No **[ ]** ? **[ ]**
Remarks:
Reference:

2.13 ADDITIONAL DATA

A. Partition co-efficient between soil/sediment and water (Kd)

Value:
Method:
GLP: Yes **[ ]** No **[ ]** ? **[ ]**
Remarks:
Reference:

B. Other data

Results: .
Remarks:
Reference:

3. ENVIRONMENTAL FATE AND PATHWAYS

*3.1.1 PHOTODEGRADATION

Type: Air **[X]**; Water **[ ]**; Soil **[ ]**; Other **[ ]**
Light source: Sunlight **[ ]**; Xenon lamp **[ ]**; Other **[ ]**
Light spectrum: . . . . . nm
Relative intensity: . . . . . *(based on intensity of sunlight)*
Spectrum of substance: . . . . . nm
Concentration of Substance: . . . . . .
Temperature: . . . . . °C
Direct photolysis:
Half life: . . . . . .
Degradation: . . . . . % (weight/weight) after . . . . . (exposure time)
Quantum yield: . . . . . .
Indirect Photolysis:
Type of sensitizer: . . . . . OH . .
Concentration of sensitizer: . .1560000 molecule/. cm^3 . . . . . .
Rate constant (radical): . . . 227.9058 E-12. cm^3/molecule*sec
Degradation: . . . . . 50% at 0.563 Hrs . . .
Method: calculated **[X]**; AOP Program (v1.89)
measured **[ ]**

GLP: Yes **[ ]** No **[X]** ? **[ ]**
Test substance:. molecular structure, purity:. . . . . .
Remarks:
Reliability: (2) valid with restrictions
Accepted calculation method
Reference: Meylan W. and Howard P. (1999) EPIWin Modeling Program. Syracuse Research Corporation. Environmental Science Center, 6225 Running Ridge Road, North Syracuse, NY 13212-2510.

*3.1.2 STABILITY IN WATER

Type: Abiotic (hydrolysis) **[X]**; biotic (sediment)**[ ]**
Half life: Not Measured
Degradation: 96% at pH 7.0 at 25 °C after 24 Hours
Method: Extraction, ABC Protocol M-8305 (1986)
GLP: Yes **[X]** No **[ ]** ? **[ ]** **Klimisch 1**
Test substance: Santoflex 14 purple liquid, Lot# KD09-813, purity:>95%
Remarks: No test substance detected at seven days. Hydrolysis products identified by GC analysis as 4-hydroxydiphenylamine (35%) and Benzoquinoneimine-n-phenyl (65%). Stock solution in acetone.
Reference: Monsanto ABC 32305, Analytical Bio-Chemistry Labs, 1986

***3.2 MONITORING DATA (ENVIRONMENTAL)** .....

Type of Measurement: Background **[ ]**; At contaminated site **[ ]**; Other **[ ]**
Media: .....
Results: .....
Remarks: .....
Reference: .....

3.3 TRANSPORT AND DISTRIBUTION BETWEEN ENVIRONMENTAL COMPARTMENTS INCLUDING ESTIMATED ENVIRONMENTAL CONCENTRATIONS AND DISTRIBUTION

***3.3.1 TRANSPORT**

Type: Adsorption **[ ]**; Desorption **[ ]**; Volatility **[ ]**; Other **[ ]**
Media:
Method:
Results:
Remarks:
Reference:

***3.3.2 THEORETICAL DISTRIBUTION (FUGACITY CALCULATION)**

Media: Air-biota **[ ]**; Air-biota-sediment-soil-water **[ ]**; Soil-biota **[ ]**; Water-air **[ ]**; Water-biota **[ ]**; Water-soil **[ ]**; Other **[ ]**
Method: Fugacity level I **[ ]**; Fugacity level II **[ ]**; Fugacity level III **[X]**; Fugacity level IV **[ ]**; Other (calculation) **[ ]**
Results:

C

	Concentration (percent)	Half-Life (hr)	Emissions (kg/hr)	Fugacity (atm)
Air	0.027	1.13	1000	7.19e-013
Water	15.2	900	1000	3.5e-014
Soil	57.5	900	1000	1.11e-015
Sediment	27.2	3.6e+003	0	2.36e-014

	Reaction (kg/hr)	Advection (kg/hr)	Reaction (percent)	Advection (percent)
Air	531	8.64	17.7	0.288
Water	375	487	12.5	16.2
Soil	1.41e+003	0	47.1	0
Sediment	168	17.4	5.58	0.58

Persistence Time: 1.06e+003 hr
Reaction Time: 1.28e+003 hr
Advection Time: 6.23e+003 hr
Percent Reacted: 82.9
Percent Advected: 17.1

Remarks:
Reliability: (2) valid with restrictions
Accepted calculation method
Reference: Meylan W. and Howard P. (1999) EPIWin Modeling Program. Syracuse Research Corporation. Environmental Science Center, 6225 Running Ridge Road, North Syracuse, NY 13212-2510.

***3.5 BIODEGRADATION**

Type:	aerobic **[X]**; anaerobic **[ ]**
Inoculum:	adapted **[X]**; non-adapted **[ ]**;
Concentration of the chemical: 20.0 mg/l related to COD **[X]**; DOC**[ ]**; test substance**[ ]**	
Medium:	water **[ ];** water-sediment **[ ];** soil **[ ];** sewage treatment **[X]**
Degradation:	0 % after 35 days
Results:	readily biodeg. **[ ];** inherently biodeg. **[]**; under test condition no biodegradation observed **[X]**, other **[ ]**
Kinetic	
Method:	ASTM Draft 3 Proposed Standard Practice for the Determination Of the Ultimate Biodegradation of Organic Chemicals (1980).
GLP:	Yes **[X]** No **[ ]** ? **[ ]** **Klimisch 1**
Test substance:	Santoflex 14 purple liquid Lot#KA01-07, purity: >95%
Remarks:	Shake Flask carbon dioxide evolution test. Glucose and Sodium Citrate used as positive controls.
Reference:	Monsanto ES-80-SS-48 MIC Environmental Sciences 1981

4. ECOTOXICITY

***4.1 ACUTE/PROLONGED TOXICITY TO FISH**

Type of test:	static **[X]**; semi-static **[ ]**; flow-through **[ ]**; other **[ ]** open-system **[ ]**; closed-system **[X]**
Species:	Salmo gairdneri (Rainbow Trout)
Exposure period:	96 Hours
Results:	LC_{50} (24h) = >1.00 mg/l LC_{50} (48h) = 0.70 mg/l LC_{50} (72h) = Not Determined LC_{50} (96h) = 0.42 mg/l NOEC = 0.18 mg/l LOEC = Not Determined
Analytical monitoring:	Yes **[X]** No **[ ]** ? **[ ]**
Method:	EPA Methods for Acute Toxicity Tests with Fish, Macroinvertebrates and Amphibians (1975)
GLP:	Yes **[X]** No **[ ]** ? **[ ]** **Klimisch 1**
Test substance:	Santoflex 14 purple liquid, purity:>95%
Remarks:	Stock solutions prepared in nanograde Acetone. Water quality parameters (pH, temperature, dissolved oxygen content) monitored throughout test. Test fish challenged with Antimycin A. Data reported at 95% confidence level.
Reference:	Monsanto ABC 30687, Analytical Bio-Chemistry Labs, 1983

Type of test:	static **[X]**; semi-static **[ ]**; flow-through **[ ]**; other **[ ]** open-system **[ ]**; closed-system **[X]**
Species:	Lepomis macrochirus (Bluegill Sunfish)
Exposure period:	96 Hours
Results:	LC_{50} (24h) = 0.38 mg/l LC_{50} (48h) = 0.30 mg/l LC_{50} (72h) = Not Determined LC_{50} (96h) = 0.30 mg/l NOEC = 0.18 mg/l LOEC = Not Determined
Analytical monitoring:	Yes **[X]** No **[ ]** ? **[ ]**
Method:	EPA Methods for Acute Toxicity Tests with Fish, Macroinvertebrates and Amphibians (1975)
GLP:	Yes **[X]** No **[ ]** ? **[ ]** **Klimisch 1**
Test substance:	Santoflex 14 purple liquid , purity:>95%
Remarks:	Stock solutions prepared in nanograde Acetone. Water quality parameters (pH, temperature, dissolved oxygen content) monitored throughout test. Test fish challenged with Antimycin A. Data reported at 95% confidence level.
Reference:	Monsanto ABC 30686, Analytical Bio-Chemistry Labs, 1983

Type of test:	static **[X]**; semi-static **[ ]**; flow-through **[ ]**; other **[ ]** open-system **[ ]**; closed-system **[X]**
Species:	Pimephales promelas (Fathead Minnows)
Exposure period:	96 Hours
Results:	LC_{50} (24h) = 1.30 mg/l LC_{50} (48h) = 1.30 mg/l LC_{50} (72h) = Not Determined LC_{50} (96h) = 1.10 mg/l NOEC = 0.32 mg/l LOEC = Not Determined
Analytical monitoring:	Yes **[X]** No **[ ]** ? **[ ]**
Method:	EPA Methods for Acute Toxicity Tests with Fish, Macroinvertebrates and Amphibians (1975)
GLP:	Yes **[X]** No **[ ]** ? **[ ]** **Klimisch 1**
Test substance:	Santoflex 14 purple liquid, purity: >96%
Remarks:	Stock solutions prepared in nanograde Acetone. Water quality parameters (pH, temperature, dissolved oxygen content) monitored throughout test. Test fish challenged with Antimycin A. Data reported at 95% confidence level.
Reference:	Monsanto ABC 31116, Analytical Bio-Chemistry Labs, 1983

4.2 ACUTE TOXICITY TO AQUATIC INVERTEBRATES

*A. Daphnia

Type of test:	static **[X]**; semi-static **[ ]**; flow-through **[ ]**; other **[ ]**; open-system **[ ]**; closed-system **[** X **]**
Species:	Daphnia magna
Exposure period:	48 Hours
Results:	EC_{50} (24h) = 0.51 mg/l

	EC_{50} (48h) = 0.20 mg/l
	NOEC = 0.10 mg/l
Analytical monitoring:	Yes **[X]** No **[ ]** ? **[ ]**
Method:	EPA Methods for Acute Toxicity Tests with Fish, Macroinvertebrates and Amphibians (1975)
GLP:	Yes **[X]** No **[ ]** ? **[ ]** **Klimisch 1**
Test substance:	Santoflex 14 purple liquid, purity: >95%
Remarks:	Stock solutions prepared in nanograde Acetone. Water quality parameters (pH, temperature, dissolved oxygen content) monitored throughout test. Data reported at 95% confidence level.
Reference:	Monsanto ABC 30688, Analytical Bio-Chemistry Labs, 1983

***4.3 TOXICITY TO AQUATIC PLANTS, e.g. algae**

Species:	Selenastrum capricurnutum (freshwater alga)
Endpoint:	Biomass **[X]**; Growth rate **[X]**; Other **[ ]**
Exposure period:	96 Hours
Results:	EC_{50} (24h) = 1.9 ppm
	EC50 (96h) = 0.7 ppm
	NOEC = 0.3 ppm
	LOEC = 0.6 ppm
Analytical monitoring:	Yes **[X]** No **[ ]** ? **[ ]**
Method:	EPA Selastrum capricornutum Printz Algal Assay Test (1978) open-system **[ ]**; closed-system **[X]**
GLP:	Yes **[X]** No **[ ]** ? **[ ]** **Klimisch 1**
Test substance:.	Santoflex 14 reddish purple gel , purity: >95%
Remarks:	Stock solutions prepared in reagent grade DMF. Concentrations determined by range-finding test. Confirmation of effect by in vivo chlorophyll a and cell numbers. Data reported at 95% confidence level.
Reference:	Monsanto BP-81-5-82 EG&G Bionomics, 1981

5. TOXICITY

*5.1 ACUTE TOXICITY

5.1.1 ACUTE ORAL TOXICITY

Type:	LD_0 **[ ]**; LD_{100} **[ ]**; LD_{50} **[X]**; LDL_0 **[ ]**; Other **[ ]**
Species/strain:	Rats, Sprague-Dawley Albino
Value:	2100 mg/kg b.w. Discriminating dose: 2510 mg/kg/bw
Method:	Defined Lethal Dose
GLP:	Yes **[ ]** No **[ ]** ? **[X]** **Klimisch 2**
Test substance:	CP-26658 Lots KC06-14 and KC06-17, purity: >95%
Remarks:	Five groups of male and female rats were fed a single oral dose of the undilated test article via oral gavage. Dosages were 1260, 1580, 2000, 2510 and 3160 mg/kg. Clinical signs of toxicity included reduced activity and appetite for 2-4 days for survivors, and increasing weakness, collapse and death for decedents in 1-4 days. Gross autopsy findings on decedents were hemorragic areas in the lungs, discolored livers and acute gastrointestinal inflammation. Survivors were sacrificed after seven days. All viscera of survivors appeared normal.
Reference:	Monsanto Y-73-169 Younger Laboratories, 1973

5.1.2 ACUTE INHALATION TOXICITY

Type:	LC_0 **[ ]**; LC_{100} **[ ]**; LC_{50} **[X]**; LCL_0 **[ ]**; Other **[ ]**
Species/strain:	Rats, Sprague-Dawley Albino
Exposure time:	6 Hours
Value:	>0.14 mg/kg
Method:	Acute Inhalation
GLP:	Yes **[ ]** No **[ ]** ? **[X]** **Klimisch 2**
Test substance:	CP-26658 liquid, purity: >95%
Remarks:	A group of four rats was exposed to the test article at a concentration of 0.14 mg/l in warm (76.5°F) air for 6 hours. All animals survived. No clinical signs of toxicity were noted.
Reference:	Monsanto Y-67-101, Younger Laboratories, 1967

5.1.3 ACUTE DERMAL TOXICITY

Type:	LD_0 **[ ]**; LD_{100} **[ ]**; LD_{50} **[X]**; LDL_0 **[ ]**; Other **[ ]**
Species/strain:	Rabbits, New Zealand Albino
Value:	>5010 mg/kg b.w.
Method:	Defined Lethal Dose
GLP:	Yes **[ ]** No **[ ]** ? **[X]** **Klimisch 2**
Test substance:	CP-26658 Lots KC06-14 and KC06-17, purity: >95%
Remarks:	The undiluted test article was applied to the shaved skin of two groups of male and female rabbits at dose levels of 5010 and 7940 mg/kg/bw. Clinical signs of toxicity noted were reduced appetite and activity for 4-7 days in survivors, and increased weakness, collapse and death at 8 days for decedents. Gross autopsy findings in decedents included hemorragic areas in the lung, liver and spleen, and discoloration of the kidneys. General gastrointestinal inflammation was also noted. Survivors were

	sacrificed after 14 days. All viscera in survivors appeared normal.
Reference:	Monsanto Y-73-169 Younger Laboratories, 1973

***5.4 REPEATED DOSE TOXICITY**

Species/strain: Rats, Sprague-Dawley Albino
Sex: Female **[ ]**; Male **[ ]**; Male/Female **[X]**; No data **[ ]**
Route of Administration: Oral/Dietary
Exposure period: One Month
Frequency of treatment: Daily
Post exposure observation period:
Dose: 0, 500, 750, 1500 and 300 ppm
Control group: Yes **[X]**; No **[ ]**; No data **[ ]**;
Concurrent no treatment **[ ]**; Concurrent vehicle**[X]**; Historical **[ ]**
NOEL: 500 ppm
LOEL: Not Determined
Results: The test article was administered to groups of 25 male and 25 female rats in a controlled study for one month. Verification of test article stability and dose levels was verified via gas chromatography. Animals were observed twice daily and weighed weekly. Overall averages for dietary concentrations were established as 0, 450, 660, 1300 and 2800 ppm. There were no mortalities during the in-life portion of the study. Toxicity during the in-life phase was indicated by a dose-related reduction of food intake and reduced body weight gains in both males and females at all dietary levels. There were no clinical signs of toxicity observed during the study. There were no gross pathology changes noted at sacrifice which were considered treatment-related, and no significant differences in liver weights or organ coloration. The NOEL for male rats was considered to be 500 ppm. The same NOEL was marginally established for female rats, even though there was a slight, but not statistically significant difference seen in average body weights.
Method: Dunnett, C.W., A Multiple Comparison Procedure for Comparing Several Treatments with a Control, Jour. Am. Stat. Assoc. 50: 1096-1121, 1955
GLP: Yes **[X]** No **[ ]** ? **[ ]** **Klimisch 1**
Test substance: Santoflex 14 dark liquid, Lot# KJ08-09, purity: >95%
Reference: Monsanto ML-87-309, Environmental Health Lab, 1987

***5.5 GENETIC TOXICITY IN VITRO**

A. BACTERIAL TEST

Type: Bacterial Reverse Mutation Assay - Ames
System of testing: Salmonella typhimurium TA-1535 TA-1537 TA-1538 TA-98 TA-100; Saccharomyces cerevisiae D4
Concentration: 0.001, 0.01, 0.1, 1.0 and 5.0 microliters/plate
Metabolic activation: With **[ ]**; Without **[ ]**; With and Without **[X]**; No data **[ ]**
Results:
Cytotoxicity conc: With metabolic activation: 5.0 ul/plate (TA-98 only)
Without metabolic activation: 5.0 ul/plate (TA-98 only)
Precipitation conc: Not Determined
Genotoxic effects:

	+	?	-
With metabolic activation:	**[ ]**	**[ ]**	**[X]**
Without metabolic activation:	**[ ]**	**[ ]**	**[X]**

Method: Ames Plate Test (Overlay method) 1975; OECD 471 equivalent

GLP:	Yes **[X]** No **[ ]** ? **[ ]** **Klimisch 1**
Test substance:	Santoflex 14 dark liquid, purity: >95%
Remarks:	The test article, in DMSO solvent, was tested directly and in the presence of liver microsomal enzyme preparations from Aroclor-induced rats. The test compound did not demonstrate mutagenic activity in any of the assasy conducted and was not considered to be mutagenic under test conditions.
Reference:	Monsanto BIO-76-229, Litton Bionetics, 1976

B. NON-BACTERIAL IN VITRO TEST

Type: Forward Mutation Mouse Lymphoma Assay
System of testing: L5178Y Mouse Lymphoma Cells
Concentration: 0.625 – 10.0 nl/ml without activation
1.25 – 60.0 nl/ml with activation
Metabolic activation: With **[ ]**; Without **[ ]**; With and Without **[X]**; No data **[ ]**
Results:
Cytotoxicity conc: With metabolic activation: 60 nl/ml
Without metabolic activation: 20 nl/ml
Precipitation conc: Not Determined
Genotoxic effects: + ? -
With metabolic activation: **[ ] [ ] [X]**
Without metabolic activation: **[ ] [ ] [X]**
Method: Clive, D., and Spector, J.F.S., Laboratory Procedure for Assessing Specific Locus Mutations at the TK Locus in Cultured L5178Y Mouse Lymphoma Cells. Mutation Res., 31:17-29, 1975
GLP: Yes **[X]** No **[ ]** ? **[ ]** **Klimisch 1**
Test substance:. Santoflex 14 dark liquid, purity: >95%
Remarks: The test compound in DMSO solution was evaluated for ability to increase mutations at the TK locus in mouse lymphoma cells at dose ranges of 0.625 to 10 nl/ml without activation and at 1.25 to 60 nl/ml with activation. Dose levels were established during a preliminary range-finding study. The dose levels selected included highly toxic treatments. Even at the highly toxic doses, the mutant frequency was comparable to negative controls. The test substance was considered to be inactive under assay conditions.
Reference: Monsanto BO-78-225, Litton Bionetics, 1979

Type: Forward Mutation Assay, CHO/HGPRT
System of testing: Chinese Hamster Ovary cells
Concentration: 1-10 ug/ml without activation
10-30 ug/ml with activation
Metabolic activation: With **[ ]**; Without **[ ]**; With and Without **[X]**; No data **[ ]**
Results:
Cytotoxicity conc: With metabolic activation: 7 ug/ml
Without metabolic activation: 5 ug/ml
Precipitation conc: Not Determined
Genotoxic effects: + ? -
With metabolic activation: **[ ] [ ] [X]**
Without metabolic activation: **[ ] [ ] [X]**
Method: CHO/HGPRT Mutation Assay (1981) Hsie, et.al.
GLP: Yes **[X]** No **[ ]** ? **[ ]** **Klimisch 1**
Test substance:. Santoflex 14 liquid Lot# KJ08-09, purity: >95%
Remarks: The mutagenic potential of Santoflex 14 was tested in cultured Chinese hamster ovary (CHO) cells. Mutation at the Hypoxanthine guanine phosphororibosyl transferase (HGPRT) locus was measured. Dosages for the test article, dissolved in Acetone, were established with a range-finding experiment. No

Chemical-related mutagenicity was observed in either the initial or the confirmation experiment, with or without S9 activation, were noted. Santoflex 14 was not mutagenic in CHO cells under any test conditions.

Reference: Monsanto ML-87-340, Environmental Health Labs, 1988

Type: In vitro Cytogenetics Study
System of testing: Chinese Hamster Ovary (CHO) cells
Concentration: 1.5 – 15.0 ug/ml
Metabolic activation: With **[ ]**; Without **[ ]**; With and Without **[X]**; No data **[ ]**
Results:
Cytotoxicity conc: With metabolic activation: 12.5 ug/ml
Without metabolic activation: 12.5 ug/ml
Precipitation conc: Not Determined
Genotoxic effects:

	+	?	-
With metabolic activation:	**[X]**	**[ ]**	**[ ]**
Without metabolic activation:	**[X]**	**[ ]**	**[ ]**

Method: Preston, Et. al., Mammalian In vivo and In vitro Cytogenics Assays: A report to the U.S. Gene-Tox Program (1981)
GLP: Yes **[X]** No **[ ]** ? **[ ]** **Klimisch 1**
Test substance:. Santoflex 14 opaque liquid #T870091, purity: >95%
Remarks: Treatment solutions were made using Acetone. Two range-Finding experiments were run to determine the optimum dose concentrations. MMS and CP were used as concurrent positive controls for treatment with and without S9 activation, respectively. Duplicate samples per treatment condition were used. Scoring for cytogenetic damage was performed on the solvent controls, positive controls, and the three highest dose levels of the test chemical. The cells were scored for both mitotic index and average cell generation time and compared to the solvent control. Average cell generation time was 12 hours for both, with a mitotic index of 5-8% Statistically significant increases in number of cells with structural aberrations and average structural aberrations/cell were observed at the 15 ug/ml level for the 48 hour harvest time and for average structural aberrations/cell at the 24 hour harvest time without S9 activation. A significant dose-response was not observed. The aberrant cells harvested at 24 and 48 hours included mainly cells with chromatid- and chromosome-type deletions, with a few decentrics and cells with chromatid interchanges. This was also observed in the solvent control. The positive MMS control yielded significant increases in both cells with structural aberrations and number of aberrations/cell. With S9 activation, a statistically significant increase in the number of cells with structural aberrations, and number of aberrations/cell was observed at the 10 ug/ml dose level, and for the number of aberrations/cell at 7.5 ug/ml and 12 hour harvest time. No dose-related response was observed. Aberrations were mainly deletions, with a few cells having chromatid interchanges, intrachanges and triradials. The positive control yielded the expected positive response. A retest confirmed results. Santoflex 14 was concluded to have a weak

clastogenicity in CHO cells under test conditions

Reference: Monsanto ML-87-341, Environmental Health Labs, 1989

*** 5.6 GENETIC TOXICITY IN VIVO**

Type: Mammalian Bone Marrow Metaphase Assay

Species/strain: Rats, Sprague-Dawley

Sex: Female **[ ]**; Male **[ ]**; Male/Female **[X]**; No data **[ ]**

Route of Administration: Oral gavage

Exposure period: 6, 18 and 30 hours

Doses: 1100 mg/kg/bw (slightly above ½ the oral LD50)

Results:

Effect on mitotic index or P/N ratio:

Genotoxic effects: + ? -
[ ] [ ] [X]

Method: Preston, Et. al., Mammalian In vivo and In vitro Cytogenics Assays: A report to the U.S. Gene-Tox Program (1981)

GLP: Yes **[X]** No **[ ]** ? **[ ]** **Klimisch 1**

Test substance: Santoflex 14 dark oil, purity: >95%

Remarks: Groups of 5 male and female rats were dosed with 1050, 1100, 1200, 1500 and 2000 mg/kg/bw in two range-finding studies. Based upon the results, a dose level of 1100 mg/kg/bw was chosen as close to the maximum tolerated dose for the metaphase analysis. During the In vivo phase, test animals were observed for pharmacotoxicity immediately after dosing, and at 6, 18 and 30 hours. Observations indicated moderate to severe pharmacotoxic signs. Two to three hours prior to sacrifice, each animal received a single intraperitoneal dose of colchicine at 4 mg/kg/bw to arrest dividing cells in metaphase. Both femurs were removed from each animal after sacrifice. The distal end was snipped off one bone and the proximal end off the other. Bone marrow cells were flushed, washed and centrifuged, and slides were prepared using freshly prepared fixative. A total of 500 well-spread metaphase cells with a minimum of overlapping chromosomes were scored for the presence of chromosome aberration per experimental treatment point (50 per animal) by two investigators (25 each per animal). Cells judged acceptable for analysis based on cell morphology and total chromosome number were further analyzed with 100x oil immersion objective where abnormalities were detected and classified. The mean number of aberrations per cell per animal was analyzed for statistically significant increases by one-tailed t tests for each time interval. Santoflex 14 did not produce significant increases in the number of aberrations or in the number of aberrant metaphases at any of the three sacrifice times evaluated. Pharmacotoxic signs observed during the study indicated that the test chemical was dosed near the maximum tolerated dose. Conclusion was that the test chemical was negative in ability to induce structural chromosomal aberrations to the hemopoietic cells of the rat bone marrow under test conditions.

Reference: Monsanto PK-88-342, Pharmakon Research, 1988

***5.8 TOXICITY TO REPRODUCTION**

Type: Fertility **[]**; One-generation study **[]**; Two-generation study **[]**; Other **[ ]**

Species/strain:

Sex: Female **[ ]**; Male **[ ]**; Male/Female **[ ]**; No data **[ ]**

Route of Administration:

Exposure period:

Frequency of treatment:

Post exposure observation period:

Premating exposure period: male: . . . . . , female:

Duration of the test:

Doses:

Control group: Yes **[ ]**; No **[ ]**; No data **[ ]**;
Concurrent no treatment **[ ]**; Concurrent vehicle **[ ]**; Historical **[ ]**

NOEL Parental:

NOEL F1 Offspring:

NOEL F2 Offspring:

Results: General parental toxicity:
Toxicity to offspring:

Method:

GLP: Yes **[ ]** No **[ ]** ? **[ ]**

Test substance: . . . . . , purity: . . . . . .

Remarks:

Reference:

***5.9 DEVELOPMENTAL TOXICITY/ TERATOGENICITY**

Species/strain:
Sex: Female **[ ]**; Male **[ ]**; Male/Female **[ ]**; No data **[ ]**
Route of Administration: .
Duration of the test:
Exposure period:
Frequency of treatment:
Doses:
Control group: Yes **[ ]**; No **[ ]**; No data **[ ]**;
Concurrent no treatment **[ ]**; Concurrent vehicle **[ ]**; Historical **[ ]**
NOEL Maternal Toxicity:
NOEL teratogenicity :
Results:
Maternal general toxicity:
Pregnancy/litter data:
Foetal data:
Method:
GLP: Yes **[ ]** No **[ ]** ? **[ ]**
Test substance: . . . . . , purity: . . . . . .
Remarks:
Reference:

5.10 OTHER RELEVANT INFORMATION

A. Specific toxicities

Type: Immunotoxicity – Repeat Insult Patch Test
Human skin, Santoflex 14 Antiozonant
Shelansky Method (Procedings of the Toilet Goods Association, No. 19, May 1953)

Results: Fifty human volunteers not previously exposed to test rubber formulations were selected. Squares soaked in the test material were applied to the arm or back and held in place with tape. Patches were removed after 24 hours and the sites examined for reactions, after which the material was reapplied. Fifteen such primary applications were made, followed by a 2-week rest period. A challenge application was then applied as before, and to the same site. No reactions were produced by either the primary or challenge applications. There was no evidence of primary irritation or skin fatigue. There was no evidence of skin sensitization under the test conditions.

Remarks: Concentration of test article was not noted. Both male and female volunteers were used in the study.

Reference: Monsanto SH-65-3, Industrial Biology Labs, 1965

Type: Immunotoxicity – Repeat Insult Patch Test
Human skin, Unvulcanized Rubber containing Santoflex 14 Antiozonant
Shelansky Method (Procedings of the Toilet Goods Association, No. 19, May 1953)

Results: Fifty one human volunteers not previously exposed to test rubber formulations were selected. The test material, in the form of 1”

squares of unvulcanized rubber, was affixed to the upper arm of each test subject and covered with gauze (occluded). Patches were removed after 24 hours and the sites examined for reactions. Direct effects by single contact were graded with a numerical score ranging from 0 (no response) to 4 (severe response) for primary irritation. Choice of contact site for the second and all subsequent applications was based on the condition of the skin at the original contact site. If irritation occurred, a different site was chosen. If no irritation occurred, the test patch was reapplied to the same site. There were 15 such applications in the induction phase of the study. Following a 14-day rest period, a challenge application was applied at the original contact site. No visible skin changes were noted on any test subject during either the induction phase or the challenge phase of the study. The test article was considered to be negative for primary skin irritation, negative for skin fatigue by sequential contact, and negative for delayed contact hypersensitivity.

Remarks: Concentration of test article in the rubber compound was 3 parts per 100 parts of SBR 1000 rubber (3 phr) Both males and females were used in the study.

Reference: Monsanto SH-67-13, Industrial Biology Labs, 1967

B. Toxicodynamics, toxicokinetics

Type:

Results:

Remarks:

References:

*** 5.11 EXPERIENCE WITH HUMAN EXPOSURE**

Results: .
Remarks: .....
Reference: .....

6. REFERENCES

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15. Monsanto ML-87-309, One Month Feeding Study of Santoflex 14 Antiozonant in Sprague-Dawley Rats, Monsanto Environmental Health Laboratories, July 7, 1988
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18. Monsanto ML-87-340, CHO/HGPRT Gene Mutation Assay with Santoflex 14, Monsanto Environmental Health Laboratories, November 28, 1988
19. Monsanto ML-87-341, In vitro Cytogenetics Study of Santoflex 14, Monsanto Environmental Health Laboratories, January 30, 1989
20. Monsanto PK-88-342, In Vivo Bone Marrow Cytogenetics Rat Metaphase Analysis, Pharmakon Research International, February 3, 1989
21. Monsanto SH-65-3, Repeated Insult Patch Test, Industrial Biology Laboratories, Inc. May 24, 1965
22. Monsanto SH-67-13, Repeated Insult Patch Test using Unvulcanized Rubber Sheets, Industrial Biology Laboratories, Inc., January 15, 1968
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I U C L I D

D a t a S e t

Existing Chemical	ID: 15233-47-3
CAS No.	15233-47-3
TSCA Name	1,4-benzenediamine, N-(1-methylheptyl)-N'-phenyl-
EINECS No.	239-281-1
Molecular Weight	296

Producer Related Part	
Company:	
Creation date:	08-NOV-2001

Substance Related Part	
Company:	
Creation date:	08-NOV-2001

Memo:	RAPA PPD Category

Printing date:	09-NOV-2001
Revision date:	
Date of last Update:	09-NOV-2001

Number of Pages:	19

Chapter (profile):	Chapter: 1, 2, 3, 4, 5, 7
Reliability (profile):	Reliability: without reliability, 1, 2, 3, 4
Flags (profile):	Flags: without flag, confidential, non confidential, WGK (DE), TA-Luft (DE), Material Safety Dataset, Risk Assessment, Directive 67/548/EEC, SIDS

1.0.1 OECD and Company Information

Type: lead organisation
Name: American Chemistry Council (formerly Chemical Manufacturers Association) Rubber and Plastics Additives (RAPA) HPV Panel
Street: 1300 Wilson Boulevard
Town: 22209 Arlington, VA
Country: United States
Phone: 703-741-5600
Telefax: 703-741-6091

08-NOV-2001

Type: cooperating company
Name: Bayer Corporation
Country: United States

08-NOV-2001

Type: cooperating company
Name: Ciba Specialty Chemicals Corporation
Country: United States

08-NOV-2001

Type: cooperating company
Name: Crompton Corporation
Country: United States

08-NOV-2001

Type: cooperating company
Name: Flexsys America L.P.
Country: United States

08-NOV-2001

Type: cooperating company
Name: Noveon, Inc (formerly BF Goodrich)
Country: United States

08-NOV-2001

Type: cooperating company
Name: R.T. Vanderbilt Company, Inc.
Country: United States

08-NOV-2001

Type: cooperating company
Name: The Goodyear Tire & Rubber Company
Country: United States

08-NOV-2001

Type: cooperating company
Name: The Lubrizol Corporation
Country: United States

08-NOV-2001

Type: cooperating company
Name: UOP, LLC.
Country: United States

08-NOV-2001

1.0.2 Location of Production Site
-

1.0.3 Identity of Recipients
-

1.1 General Substance Information

Substance type: organic
Physical status: liquid
Purity: > 95 % w/w
08-NOV-2001

1.1.0 Details on Template
-

1.1.1 Spectra
-

1.2 Synonyms

N-phenyl - N'-(1-methylhepyl)-p-phenylenediamine
08-NOV-2001

UOP 688 Antiozonant
08-NOV-2001

1.3 Impurities
-

1.4 Additives
-

1.5 Quantity
-

1.6.1 Labelling
-

1.6.2 Classification
-

1.7 Use Pattern
-

1.7.1 Technology Production/Use
-

1.8 Occupational Exposure Limit Values
-

1.9 Source of Exposure
-

1.10.1 Recommendations/Precautionary Measures
-

1.10.2 Emergency Measures
-

1.11 Packaging
-

1.12 Possib. of Rendering Subst. Harmless
-

1.13 Statements Concerning Waste
-

1.14.1 Water Pollution
-

1.14.2 Major Accident Hazards
-

1.14.3 Air Pollution
-

1.15 Additional Remarks
-

1.16 Last Literature Search
-

1.17 Reviews
-

1.18 Listings e.g. Chemical Inventories
-

2.1 Melting Point

Value:
Remark: Unknown, no studies available
08-NOV-2001

2.2 Boiling Point

Value: 431 degree C at 1013 hPa
Method: other: no data
GLP: no
08-NOV-2001 (1)

2.3 Density

Type: relative density
Value: 1.003 at 15.6 degree C
Method: other: no data
GLP: no
Result: Specific gravity = 1.003
08-NOV-2001 (1)

2.3.1 Granulometry
-

2.4 Vapour Pressure

Value:
Remark: Unknown, no studies available
08-NOV-2001

2.5 Partition Coefficient

log Pow:
Method: OECD Guide-line 107 "Partition Coefficient (n-octanol/water), Flask-shaking Method"
Year:
Result: Method not applicable.
Reliability: (1) valid without restriction
Guideline study
Flag: Critical study for SIDS endpoint
08-NOV-2001 (2)

2.6.1 Water Solubility

Qualitative: not soluble
Method: OECD Guide-line 105 "Water Solubility"
Remark: Evaluation as part of Certificate of Analysis
Result: Insoluble;
pH Value, pKa Value: Unknown, no studies available
Reliability: (1) valid without restriction
Guideline study
Flag: Critical study for SIDS endpoint
08-NOV-2001 (2)

2.6.2 Surface Tension
-

2.7 Flash Point
-

2.8 Auto Flammability
-

2.9 Flammability
-

2.10 Explosive Properties
-

2.11 Oxidizing Properties

Result:
Remark: Unknown, no studies available
08-NOV-2001

2.12 Additional Remarks

Memo: Fat Solubility
Method: OECD 116
Result: 100%
08-NOV-2001 (2)

3.1.1 Photodegradation

Type: air
INDIRECT PHOTOLYSIS
Sensitizer: OH
Conc. of sens.: 1560000 molecule/cm3
Rate constant: .000000000229 cm3/(molecule * sec)
Degradation: 50 % after .6 hour(s)
Method: other (calculated): AOP Program (v1.89)
Year: 1999 GLP: no
Test substance: other TS: molecular structure
Reliability: (2) valid with restrictions
Acceted calculation method
Flag: Critical study for SIDS endpoint
08-NOV-2001 (3)

3.1.2 Stability in Water
-

3.1.3 Stability in Soil
-

3.2 Monitoring Data (Environment)
-

3.3.1 Transport between Environmental Compartments

Type: fugacity model level III
Media: other: air - water - soil - sediment
Air (Level I):
Water (Level I):
Soil (Level I):
Biota (L.II/III):
Soil (L.II/III):
Method: other: EPIWIN, Level III Fugacity Model
Year: 1999
Result:

Media	Concentration (percent)	Half-Life (hr)	Emissions (kg/hr)	Fugacity (atm)
Air	0.0248	1.12	1000	7.34e-013
Water	8.94	900	1000	2.61e-014
Soil	43.4	900	1000	3.56e-016
Sediment	47.6	3.6e+003	0	1.76e-014

Media	Reaction (kg/hr)	Advection (kg/hr)	Reaction (percent)	Advection (percent)
Air	615	9.94	20.5	0.331
Water	275	358	9.18	11.9
Soil	1.34e+003	0	44.6	0
Sediment	367	38.1	12.2	1.27

Persistence Time: 1.33e+003 hr

Reaction Time: 1.54e+003 hr
Advection Time: 9.86e+003 hr
Percent Reacted: 86.5
Percent Advected: 13.5
Reliability: (2) valid with restrictions
Acceted calculation method
Flag: Critical study for SIDS endpoint
08-NOV-2001 (3)

3.3.2 Distribution
-

3.4 Mode of Degradation in Actual Use
-

3.5 Biodegradation
-

3.6 BOD5, COD or BOD5/COD Ratio
-

3.7 Bioaccumulation
-

3.8 Additional Remarks
-

AQUATIC ORGANISMS

4.1 Acute/Prolonged Toxicity to Fish

Type: other
Species: other: Freshwater fish
Exposure period: 96 hour(s)
Unit: mg/l Analytical monitoring: no
LC50: .067
Method: other: ECOSAR Program (v0.99e)
Year: 1999 GLP: no
Test substance: other TS: molecular structure
Remark: Chemical may not be soluble enough to measure this predicted effect.
Reliability: (2) valid with restrictions
Acceted calculation method
Flag: Critical study for SIDS endpoint
08-NOV-2001 (3)

Type: other
Species: other: Saltwater fish
Exposure period: 96 hour(s)
Unit: mg/l Analytical monitoring: no
LC50: .094
Method: other: ECOSAR Program (v0.99e)
Year: 1999 GLP: no
Test substance: other TS: molecular structure
Remark: Chemical may not be soluble enough to measure this predicted effect.
Reliability: (2) valid with restrictions
Acceted calculation method
Flag: Critical study for SIDS endpoint
08-NOV-2001 (3)

4.2 Acute Toxicity to Aquatic Invertebrates

Type: other
Species: Daphnia sp. (Crustacea)
Exposure period: 48 hour(s)
Unit: mg/l Analytical monitoring: no
LC50 : .093
Method: other: ECOSAR Program (v0.99e)
Year: 1999 GLP: no
Test substance: other TS: molecular structure
Remark: Chemical may not be soluble enough to measure this predicted effect.
Reliability: (2) valid with restrictions
Acceted calculation method
Flag: Critical study for SIDS endpoint
08-NOV-2001 (3)

Type: other
Species: Mysidopsis bahia (Crustacea)
Exposure period: 96 hour(s)
Unit: mg/l Analytical monitoring: no
LC50 : .00134
Method: other: ECOSAR Program (v0.99e)
Year: 1999 GLP: no
Test substance: other TS: molecular structure
Reliability: (2) valid with restrictions
Acceted calculation method
08-NOV-2001 (3)

4.3 Toxicity to Aquatic Plants e.g. Algae

Species: other algae: Green algae
Endpoint:
Exposure period: 96 hour(s)
Unit: mg/l Analytical monitoring: no
EC50: .072
Method: other: ECOSAR Program (v0.99e)
Year: 1999 GLP: no
Test substance: other TS: molecular structure
Remark: Chemical may not be soluble enough to measure this predicted effect.
Reliability: (2) valid with restrictions
Acceted calculation method
Flag: Critical study for SIDS endpoint
08-NOV-2001 (3)

4.4 Toxicity to Microorganisms e.g. Bacteria
-

4.5 Chronic Toxicity to Aquatic Organisms

4.5.1 Chronic Toxicity to Fish
-

4.5.2 Chronic Toxicity to Aquatic Invertebrates
-

TERRESTRIAL ORGANISMS

4.6.1 Toxicity to Soil Dwelling Organisms
-

4.6.2 Toxicity to Terrestrial Plants
-

4.6.3 Toxicity to other Non-Mamm. Terrestrial Species
-

4.7 Biological Effects Monitoring
-

4.8 Biotransformation and Kinetics
-

4.9 Additional Remarks
-

5.1 Acute Toxicity

5.1.1 Acute Oral Toxicity

Type:	LD50
Species:	rat
Strain:	other: Holtzman
Sex:	male
Number of Animals:	5
Vehicle:	other: corn oil
Value:	4.3 mg/kg bw
Method:	other: Method described by Weil, C.S., Biometrics 8, 249, 1952
Year:	1952 GLP: no
Test substance:	other TS: Commercial product, >95% purity
Method:	UOP 688 was administered orally to six groups , each composed of 5 male albino rats, weight range 219-251 grams. Each dose was administered either undiluted or as a 10% volume/volume solution in corn (Mazola) oil. Dosage levels tested were 0.046, 0.10, 2.15, 4.46, 10.0, and 21.5 mg/kg body weight. All animals were observed closely for gross signs of systemic toxicity and mortality during the day of dosage, and at least once daily thereafter for 14 days. All animals were subject to gross necropsy at study termination.
Result:	Animals in the 0.046, 0.1, and 2.15 mg/kg dosage levels generally exhibited normal appearance and behaviour throughout the 14 day period. Rats at the 4.64 mg/kg dose level began showing depression, slowed righting reflexes, and diarrhea on the second day following dosage. On the fourth day after dosage, one rat showed labored respiration, ataxia, depressed righting, placement, and pain reflexes, and a marked bloody nasal discharge. These signs generally continued until death occurred, or until the fifth day following dosage when the two surviving rats appeared normal. The rats in the 10.0 and 21.5 mg/kg doe levels showed diarrhea, unkempt fur, depression, depressed relexes, and a dark oily stain in the perineal area on the day after dosage. These signs continued until death occurred. Death was preceded by lacrimation and coma.
Reliability:	(2) valid with restrictions Meets generally accepted scientific standards, well documented and acceptable for assessment
Flag:	Critical study for SIDS endpoint

08-NOV-2001 (4)

5.1.2 Acute Inhalation Toxicity

Type:
Species:
Strain:
Sex:
Number of
Animals:
Vehicle:
Exposure time:
Value:
Method:
Year: GLP:
Test substance:
Remark: Unknown, no studies available.
Not an appropriate route of exposure due high boiling point.
08-NOV-2001

5.1.3 Acute Dermal Toxicity

Type: LD50
Species: rabbit
Strain: New Zealand white
Sex: male/female
Number of
Animals: 10
Vehicle:
Value: > 2000 mg/kg bw
Method: other: U.S. Code of Federal Regulations 40 CFR 163
Year: GLP:
Test substance: other TS: Commercial product, >95% purity
Method: The test material was applied to five male and five female white New Zealand white rabbits. The dose was applied to the abdominal skin which had been previously been shaven. The abdominal skin area of all the rabbits was abraded by making a series of longitudinal minor epidermal incisions placed two to three centimeters apart, using a hypodermic needle as a cutting tool. The abrasions were sufficiently deep to penetrate the epidermis, but not to induce bleeding. The undiluted sample was applied at a dosage level of 2.0 grams/kg of body weight. The test sample was kept in contact with the skin on at least 10% of the body surface. During the exposure period, each rabbit was observed for signs of toxicity at two, four and five and one half hours post application. After 23 ¾ to 24 hours of skin contact exposure, any unabsorbed sample remaining on the skin was removed by gentle sponging with a moistened towel. Rabbits were observed for 14 days following completion of the exposure period. Examinations for gross signs of systemic toxicity were carried out twice daily during this period. At the end of the 14 day observation period, rabbits were weighted, sacrificed and gross necropsy was performed.
Remark: study reviewed by lab QA Director
Result: One female rabbit was found dead on day two. Necropsy

revealed diarrhea stains around the anus, congested lungs, a mottled and darkened liver, stomach and intestine which appeared autolytic and pale but congested kidneys. Erythemia and edema followed by desquamation and atonia were seen at the application site in all surviving animals. Four rabbits exhibited spotted whitening on the day of exposure completion. Systemic effects were limited to transient nasal discharge in two animals and transient green colored urine in one animal.
Reliability: (1) valid without restriction
Meets National standards method
Flag: Critical study for SIDS endpoint
08-NOV-2001 (5)

5.1.4 Acute Toxicity, other Routes
-

5.2 Corrosiveness and Irritation

5.2.1 Skin Irritation

Species: rabbit
Concentration:

Exposure: Semiocclusive
Exposure Time: 24 hour(s)
Number of Animals: 6
PDII: 1.5
Result:
EC classificat.:
Method: other: U.S. Code of Federal Regulations 40 CRF 163
Year: GLP:
Test substance: other TS: Commercial product, >95% purity
Method: 0.5 ml undiluted test material was applied under one inch square surgical gauze patches to two abraded skin areas and two intact skin areas on each of six New Zealand White rabbits. After 24 hours of skin contact exposure, any unabsorbed sample remaining on the skin was removed by gentle sponging with a moistened towel. The reactions were scored immediately after removal of the patches (24 hour reading), and again two days later (72 hour reading).
Remark: study reviewed by lab QA Director
Result: Irritative effects noted during the course of the study included very slight to well defined erythema, at the abraded and intact sites of all animals. Very slight to slight edema scores were noted in five animals on the abraded and intact sites. The Primary Irritation Index was found to be 1.5. Some loss of skin resiliency (atonicity) was noted. No evidence of corrosivity was observed.
Reliability: (1) valid without restriction
Meets National standards method
09-NOV-2001 (5)

Species: rabbit
Concentration: undiluted

Exposure: Semiocclusive
Exposure Time:
Number of
Animals: 6
PDII:
Result:
EC classificat.:
Method: other: U.S. Code of Federal Regulations 49 CFR 173.136 -137
Year: 1992 GLP: yes
Test substance: other TS: Commercial product, Lot #0483, >95% purity
Method: The primary dermal irritation/corrosivity potential was evaluated when applied to the skin of 3 male and 3 female rabbits under 3 minute, 1 hour, and 4 hour semi-occluded conditions. Each application site was examined for erythemia and edema according to the Draize method.
Result: No evidence of corrosion was observed at any of the test sites for any of the exposure periods.

Not considered corrosive to the skin of rabbits
Reliability: (1) valid without restriction
GLP Guideline study
09-NOV-2001 (6)

5.2.2 Eye Irritation

Species: rabbit
Concentration: undiluted
Dose: .1 ml
Exposure Time:
Comment: other: see method
Number of
Animals: 9
Result:
EC classificat.:
Method: other: U.S. Code of Federal Regulations 40 CFR 163
Year: GLP:
Test substance: other TS: Commercial product, >95% purity
Method: 0.1 ml of the undiluted test material was applied to the left or right eye of each of nine rabbits. The opposite eye served as a control. The treated eyes of six rabbits were left unrinsed. The treated eye of three rabbits were rinsed after 30 seconds for 60 seconds with 200 ml of lukewarm water. Examinations for gross signs of eye irritation were made approximately 24, 43, and 70 ½ hours and four, seven, ten, thirteen, sixteen, and nineteen days following application. Scoring of irritative effects was according to the method of Draize.
Remark: study reviewed by lab QA Director
Result: Non-rinsed eyes - Irritative effects noted during the study included isolated occurrences of mild corneal opacity with up to one-quarter of the corneal area involved in the two

rabbits. Conjuctival effects included isolated occurrences of mild erythema in five rabbits. Total irritation score ranged from 0-5.

Rinsed eyes - Mild corneal irritation was observed in the rinsed eye group. These effects generally cleared after four days post-treatment with opacity occurring once after this reading in one rabbit. Sporadic occurrences of mild to moderate conjunctival irritation on days 13 and 19 were noted in three rabbits. The total irritation scores ranged from 0-7.

09-NOV-2001 (5)

5.3 Sensitization

Type:	Patch-Test
Species:	human
Number of Animals:	15
Vehicle:	other: acetone
Result:	not sensitizing
Classification:	not sensitizing
Method:	other: Adapted from the repeated insult patch test procedure described by Draize (Appraisal of the Safety of Chemicals in Foods, Drugs, and Cosmetics, pp. 52-55, The Association of Food and Drug Officials of the United States, 1959)
Year:	GLP: no
Test substance:	other TS: Commercial product
Method:	0.1 ml of a 20% acetone solution of the sample (equivalent to 20 mg of the test material) was applied to a ¾ x 7/8 inch piece of filter paper. After the acetone had evaporated, the filter paper was place on the skin of 15 human subjects. Nine patch applications were made to the same location on the upper arm over a period of two weeks. A challenge patch was applied to skin area not previously exposed to the test material.
Result:	None of the 15 subjects tested exhibited any evidence of sensitization.

09-NOV-2001 (7)

5.4 Repeated Dose Toxicity

-

5.5 Genetic Toxicity 'in Vitro'

Type:	Ames test
System of testing:	Salmonella typhimurium strains TA-1535, TA-1537, TA-1538, TA-98, and TA-100
Concentration:	0.0005, 0/001, 0.0025, 0.005, 0.01, 0.05, 0.1, 0.5 ug/plate
Cytotoxic Conc.:	Without metabolic activation: >0.07 ug/plate; Precipitation conc: 0.59 ug/plate
Metabolic activation:	with and without
Result:	negative
Method:	other: Ames Salmonella/Microsome Plate Test, Protocol 401, Edition 14
Year:	GLP: yes
Test substance:	other TS: Commercial product, purity >95%
Remark:	Examination of mutagenic activity in the presence and absence of liver microsomal preparations was conducted. Solvent control (dimethyl sulfoxide) and specific positive control compounds were assayed concurrently with the test material. The concurrent solvent control data were used as a basis for evaluating results.
Result:	The test material did not exhibit genetic activity in any of the assays conducted and was not mutagenic to the S. typhimurium indicator organism under the test conditions.
Reliability:	(1) valid without restriction GLP Guideline study
Flag:	Critical study for SIDS endpoint

09-NOV-2001 (8)

5.6 Genetic Toxicity 'in Vivo'

-

5.7 Carcinogenicity

-

5.8 Toxicity to Reproduction

-

5.9 Developmental Toxicity/Teratogenicity

-

5.10 Other Relevant Information

-

5.11 Experience with Human Exposure

-

(1) From internal technical bulletin, 1981

(2) Evaluation as part of Certificate of Analysis, by Fine Pharmaceutical Laboratories, Ltd., Hamilton, Ontario, Canada, January 24, 2001

(3) Meylan W. and Howard P. (1999) EPIWin Modeling Program. Syracuse Research Corporation. Environmental Science Center, 6225 Running Ridge Road, North Syracuse, NY 13212-2510.

(4) Unpublished study, "Acute Oral Adminstration of UOP 604 and UOP 688 to Rats", Hill Top Research Institute, Inc. Miamiville, OH, February 13, 1963

(5) Unpublished study, "Acute Dermal Toxicity, Primary Skin Irritation and Acute Eye Irritation Potential of UOP 688", Hill Top Research, Inc., Cincinnati, OH, September 22, 1981

(6) Unpublished study, "Skin Corrosivity Study of UOP 688 in Rabbits (DOT/UN Regulations)", Hazelton Wisconsin, Inc, Madison WI, June 25, 1993.

(7) Unpublished study, "Repeated Insult Patch Test of UOP 688 and 12267", Hill Top Research, Inc., September 20, 1962.

(8) Unpublished study, "Mutagenicity Test on XPA-28-86/UOP 688 in the Ames Salmonella/Micorsomal Reverse Mutation Assay", Hazelton Laboratories America, Inc., Kensington, MD, October 13, 1981.

7.1 End Point Summary

-

7.2 Hazard Summary

-

7.3 Risk Assessment

-

I U C L I D

D a t a S e t

Existing Chemical	ID: 68953-84-4
CAS No.	68953-84-4
EINECS Name	N,N'-diaryl-p-phenylenediamines
EINECS No.	273-227-8

Producer Related Part	
Company:	Goodyear Chemicals Europe
Creation date:	06-APR-1998
Substance Related Part	
Company:	Goodyear Chemicals Europe
Creation date:	06-APR-1998

Printing date:	30-OCT-2001
Revision date:	
Date of last Update:	20-FEB-2001

Number of Pages:	28

Chapter (profile):	Chapter: 2.1, 2.2, 2.4, 2.5, 2.6.1, 3.1.1, 3.1.2, 3.3.1, 3.5, 4.1, 4.2, 4.3, 5.1.1, 5.1.2, 5.1.3, 5.1.4, 5.4, 5.5, 5.6, 5.8, 5.9
Reliability (profile):	Reliability: 1, 2
Flags (profile):	Flags: without flag, confidential, non confidential, WGK (DE), TA-Luft (DE), Material Safety Dataset, Risk Assessment, Directive 67/548/EEC, SIDS

2.1 Melting Point

Value: 90 - 105 degree C
Decomposition: ambiguous
Method: other: ASTM D-1519
Year: 1993
GLP: no
Reliability: (2) valid with restrictions
Although this study was probably not conducted to GLP, the test parameters used were based on a known and well established procedure.
31-JUL-2000 (34)

2.2 Boiling Point
-

2.4 Vapour Pressure
-

2.5 Partition Coefficient

log Pow: 3.4 - 4.3
Method: OECD Guide-line 117 "Partition Coefficient (n-octanol/water), HPLC Method"
Year: 1995
GLP: yes
Remark: The product exhibits much lower values than DDT (6.2) which provides a benchmark for highly bioaccumulative chemicals. The test substance contains 3 major components.
Result: # Methyl Groups -0 log Pow 3.37
Methyl Groups -1 log Pow 3.82
Methyl Groups -2 log Pow 4.28

The major components of the test substance displayed partion coefficients between 3.4 and 4.3.
Reliability: (1) valid without restriction
01-AUG-2000 (28)

log Pow: > 3.7 at 22.8 degree C
Method: other (measured)
Year: 1992
GLP: yes
Remark: for N,N'-Diphenyl-p-phenylenediamine
Reliability: (1) valid without restriction

20-FEB-2001 (9)

log Pow: > 4.3 at 22.8 degree C
Method: other (measured)
Year: 1992
GLP: yes
Remark: For N-phenyl-N'-(o-tolyl)-p-phenylenediamine
Reliability: (1) valid without restriction
31-JUL-2000 (9)

log Pow: > 4.6 at 22.8 degree C
Method: other (measured)
Year: 1992
GLP: yes
Remark: For N,N'-Di(o-tolyl)-p-phenylenediamine
Reliability: (1) valid without restriction
20-FEB-2001 (9)

2.6.1 Water Solubility
-

3.1.1 Photodegradation
-

3.1.2 Stability in Water

Type:
Method:
Year: 1994 GLP: yes
Test substance: as prescribed by 1.1 - 1.4
Remark: See Biodegradation Studies
Reliability: (1) valid without restriction
31-JUL-2000

3.3.1 Transport between Environmental Compartments
-

3.5 Biodegradation

Type: anaerobic
Inoculum: activated sludge, domestic
Concentration: 100 mg/l related to Test substance
Degradation: .64 % after 28 day
Result: other: not readily biodegradable
Method: OECD Guide-line 301 F "Ready Biodegradability: Manometric Respirometry Test"
Year: 1994 GLP: yes
Test substance: as prescribed by 1.1 - 1.4
Reliability: (1) valid without restriction
31-JUL-2000 (22)

Type: anaerobic
Inoculum: activated sludge
Degradation: 0 % after 28 day
Method: other: OECD 301 Manometric Respirometry, modified according to

EEC Round RobinTest "Assessment of Respirometry" DGX 1/283/82 Rev. 6, EEC Directive 79/831, Annex V, Part C

Year: 1990 GLP: yes

Test substance: as prescribed by 1.1 - 1.4

Reliability: (1) valid without restriction

31-JUL-2000 (6)

AQUATIC ORGANISMS

4.1 Acute/Prolonged Toxicity to Fish

Type: flow through

Species: Cyprinus carpio (Fish, fresh water)

Exposure period: 14 day

Unit: mg/l Analytical monitoring: yes

NOEC: .28

LC50: .43

Method: OECD Guide-line 204 "Fish, Prolonged Toxicity Test: 14-day Study"

Year: 1996 GLP: yes

Test substance: other TS

Method: Test water was generated by adding the test substance in acetone to a larger volume of water which was stirred, allowed to settle, and then siphoned to a stock solution holding tank. This stock solution was then metered into exposure tanks for the fish experiments. A range-finding trial exposed carp to to nominal levels of 2.5, 5, 10, and 25 mg/L (ppm) of the test substance. Survival rates were up to 80% within the first 48 hours for the three (3) highest dose levels and the 2.5 mg/L induced no mortality in the first 48 hours although 90% deaths were seen through Day six (6).

In the definitive phase, duplicate test tanks contained 10 carp each and the test substance nominal concentrations of 0, 0.1, 0.23, 0.51, 1.1, and 2.5 mg/L (ppm). Chemical analysis (HPLC) of the test substance in the test tanks on Days -0, -3, -7, and -14 showed that mean concentrations for the 14-day test period were 0.053, 0.12, 0.19, 0.28, and

0.67 mg/L (ppm). Fish densities were 0.35 g biomass/L flowing test solution per day. Tank volume turnover for the flow-through system was 6.5/day. Carp were monitored daily for mortality and signs of erratic swimming behavior for 14 days during exposure. Body weights and lengths were recorded for representative fish prior to study initation, and on all test fish on Day 14. A LC50 value was then calculated.

Result: Carp died only at the highest test substance concentration; 2/20 on Day-3, 7/20 on Day-7, and 20/20 by Day-14. Other findings at the 0.67 mg/L (ppm) level included darkened pigmentation on the fish (likely due to adsorption of the test chemical), lethargic swimming behavior, and loss of equilibrum. There were no test substance-related effects on body lengths or weights.

Test substance: Tested as the commercial product

Reliability: (1) valid without restriction

20-FEB-2001 (29)

Type: flow through

Species: Oncorhynchus mykiss (Fish, fresh water)

Exposure period: 14 day

Unit: mg/l Analytical monitoring: yes

NOEC: .14

LC50: .26

Method: OECD Guide-line 204 "Fish, Prolonged Toxicity Test: 14-day Study"

Year: 1997 GLP: yes

Test substance: as prescribed by 1.1 - 1.4

Method: Test water was generated by adding the test substance in acetone to a larger volume of water which was stirred, allowed to settle, and then siphoned to a stock solution holding tank. This stock solution was then metered into exposure tanks for fish experiments. A preliminary study in trout was performed using nominal concentrations of the test substance of 0.1, 0.23, 0.51, 1.1, and 2.5 mg/L. Mortality rates were 100% at the highest level by Day-3, and was 80% by Day-7 at 1.1 mg/L.

In the definitive phase, duplicate test tanks contained 10 trout each, Test substance nominal concentrations of 0, 0.094, 0.19, 0.38, 0.75, and 1.5 mg/L (ppm) were chosen. Chemical analysis (HPLC) of the test substance in the test tanks on Days -0, -7 and -14 showed that mean concentrations for the 14-day test period were 0.062, 0.093, 0.14, 0.35, and 0.66 mg/L (ppm). Fish densities were 0.079 g biomass/L

flowing test solution per day. Tank volume turnover for the flow-through system was 6.5/day. Fish were monitored daily for mortality and signs of erratic swimming behavior for 14-days during exposure. Body weights and lengths were recorded for representative fish prior to study initiation, and on all test fish on Day-14. LC50 values were calculated for 96-hours and 14-days.

Result: Fish died only at 0.35 and 0.66 mg/L concentrations; 0/20 and 1/20 died by Day-2 and 1/20 and 19/20 by Day -4 , respectively. Further, 100 % of the high dose (0.66 mg/L) fish died by Day-5 and 17/20 of the 0.37 mg/L fish by Day-14. Other findings at the two highest levels included darkened pigmentation of the fish, lethargic swimming behavior, and loss of equilibrium. There were test substance-related effects on 14-day body lengths and weights in the 0.35 mg/L group. The calculated LC50 for the test substance in the study at 96-hours was 0.48 mg/L and 0.26 mg/L at 14-days. The No Observed Effect Concentration (NOEC) was 0.14 mg/L at 96-hours and 14-days.

Reliability: (1) valid without restriction

31-JUL-2000 (37)

4.2 Acute Toxicity to Aquatic Invertebrates

Type:
Species: Daphnia magna (Crustacea)
Exposure period: 48 hour(s)
Unit: mg/l Analytical monitoring: yes
NOEC: .36
EC50: 1.8
Method: OECD Guide-line 202, part 1 "Daphnia sp., Acute Immobilisation Test"
Year: 1996 GLP: yes
Test substance: other TS
Method: A range-finding study used ten (10) 24-hour old daphnids exposed to nominal levels of 0, 13,22,36,60, and 100 mg/L of the test substance. Immpbilization (15%) of the daphnids occurred at the highest level (100 mg/L). Sublethal lethargy was observed at all but the lowest test concentration (13 mg/L). Brown matter, apparently the test substance since brown precipitate was observed in the media, was observed to adhere to both surviving and non-surviving daphnids.

In the definitive phase, duplicate aquaria containing 10

daphnids each and test substance nominal concentrations of 0, 1.3, 2.2, 3.6, 6.0 and 10 mg/L (ppm) were prepared. Mean values for the test substance concentrations in the test media were determined by averaging chemical analyses (HLPC) of 0-hours and 48-hours.

Daphnia immobilization and aquaria observations were made at 24- and 48-hours following the study initation. From these data, an Effective Concentration in one-half the organisims (EC50) and a No Observed Effect Concentration (NOEC) were estimated.

Result: Measured concentrations of the test substance ranged from 19 to 29% of nominal levels. At the highest concentration (1.8 mg/L), 25 % of the daphnids were immobilized at 48-hours of exposure. For the 0.68 and 1.1 mg/L groups, Five (5) % of the daphnids were immobile. No immobilization was observed at 0.20 and 0.36 mg/L exposures. Lethargic activity was not observed at any treatment level. Brown particulates, perhaps the test substance, were observed to adhere to the test daphnids, with some buoyed to the surface of the aquaria by this particulate material. The results indicated that the EC50 for the test substance was 1.8 mg/L. The No Observed Effect Concentration (NOEC) was shown to be 0.36 mg/L.

Test substance: Tested as the commercial product

Reliability: (1) valid without restriction

31-JUL-2000 (27)

4.3 Toxicity to Aquatic Plants e.g. Algae

Species: Selenastrum capricornutum (Algae)
Endpoint: biomass
Exposure period: 72 hour(s)
Unit: µg/l Analytical monitoring: yes
NOEC: 4.3
EC10: 4.3
EC50: 18
Method: OECD Guide-line 201 "Algae, Growth Inhibition Test"
Year: 1996 GLP: yes
Test substance: other TS
Method: A range-finding trial used nominal levels of 0, 1,10, 100, and 1000 ug/L (ppb) of the test substance and a solvent control in algae cultures (approximately 1x104 cells per flask). Following 72-hours incubation, algal cell densities were determined using a hemacytometer. Values were

127,76,109,69 and 1%, respectively, of the solvent control response. These values were used to set exposures for the definitive phase.

In the definitive phase, triplicate algal cultures were exposed to the test substance at nominal concentrations of 16, 31, 63,130, 250, and 500 ug/L (ppb). Cell densities were monitored at 24-, 48-, and 72-hours following study initiation. From these data, EC50 (50% decrease) values for Biomass (EbC50) and Growth Rate (ErC50) were calculated. Test substance concentrations in the test media were determined at 0- and 72-hours using HLPC. The mean concentrations were 7.5, 13, 14, 28, 50, and 79 ug/L (ppb).

Result: The inhibitions of algae Growth Rates for the test substance in the definitive 72-hour study were 0, 2, 15, 20, 32, and 38% (relative to pooled control values) for the measured test substance concentrations of 7.5, 13, 14, 28, 50, and 79 ug/L (ppb). Corresponding inhibitions of Biomass generation were 15, 41, 59, 63, 81, and 91%. Individual cell appearances were found microscopically to be normal for surviving cells except cellular bloating was noted at the highest exposure level. Calculations indicated that the ErC50 for the test substance was > 79 ug/L (ppb) while the EbC50 was 18 ug/L (ppb). The No Observed Effect Concentrations (NOECs) were assumed to be equivalent to EC10 values, and accordingly were EbC10 = 4.3 ug/L (ppb) and ErC10= 31 ug/L (ppb).

The EC50 values for the test substance ranged from 18 to > 79 ug/l (ppb) for Biomass increases and Growth Rates. The NOECs ranged from 4.3 to 31 ug/L (ppb) for these parameters.

Test substance: Tested as the commercial product

Reliability: (1) valid without restriction

31-JUL-2000 (30)

Species: Selenastrum capricornutum (Algae)
Endpoint: growth rate
Exposure period: 72 hour(s)
Unit: µg/l Analytical monitoring: yes
NOEC: 31
EC10: 31
EC50: > 79
Method: OECD Guide-line 201 "Algae, Growth Inhibition Test"
Year: 1996 GLP: yes
Test substance: other TS
Method: A range-finding trial used nominal levels of 0, 1,10, 100, and 1000 ug/L (ppb) of the test substance and a solvent

control in algae cultures (approximately 1x104 cells per flask). Following 72-hours incubation, algal cell densities were determined using a hemacytometer. Values were 127,76,109,69 and 1%, respectively, of the solvent control response. These values were used to set exposures for the definitive phase.

In the definitive phase, triplicate algal cultures were exposed to the test substance at nominal concentrations of 16, 31, 63,130, 250, and 500 ug/L (ppb). Cell densities were monitored at 24-, 48-, and 72-hours following study initiation. From these data, EC50 (50% decrease) values for Biomass (EbC50) and Growth Rate (ErC50) were calculated. Test substance concentrations in the test media were determined at 0- and 72-hours using HLPC. The mean concentrations were 7.5, 13, 14, 28, 50, and 79 ug/L (ppb).

Result: The inhibitions of algae Growth Rates for the test substance in the definitive 72-hour study were 0, 2, 15, 20, 32, and 38% (relative to pooled control values) for the measured test substance concentrations of 7.5, 13, 14, 28, 50, and 79 ug/L (ppb). Corresponding inhibitions of Biomass generation were 15, 41, 59, 63, 81, and 91%. Individual cell appearances were found microscopically to be normal for surviving cells except cellular bloating was noted at the highest exposure level. Calculations indicated that the ErC50 for the test substance was > 79 ug/L (ppb) while the EbC50 was 18 ug/L (ppb). The No Observed Effect Concentrations (NOECs) were assumed to be equivalent to EC10 values, and accordingly were EbC10 = 4.3 ug/L (ppb) and ErC10= 31 ug/L (ppb).

The EC50 values for the test substance ranged from 18 to > 79 ug/l (ppb) for Biomass increases and Growth Rates. The NOECs ranged from 4.3 to 31 ug/L (ppb) for these parameters.

Test substance: Tested as the commercial product
Reliability: (1) valid without restriction
31-JUL-2000 (30)

5. Toxicity

5.1 Acute Toxicity

5.1.1 Acute Oral Toxicity

Type: LD50
Species: rat
Strain:

Sex: no data
Number of Animals:
Vehicle:
Value: > 2000 mg/kg bw
Method: other: Directive 84/49/EEC, B.1
Year: 1990 GLP: yes
Test substance: as prescribed by 1.1 - 1.4
Reliability: (1) valid without restriction
01-AUG-2000 (7)

Type: LD50
Species: rat
Strain:
Sex: male/female
Number of Animals: 10
Vehicle: other: corn oil
Value: > 5000 mg/kg bw
Method: other: US EPA 40CFR798.2650, Oral Toxicity-Limit Test
Year: 1993 GLP: yes
Test substance: as prescribed by 1.1 - 1.4
Method: Five (5) male and five (5) female young adult rats (Sprague-Dawley) were administered a single dose of the test substance by gavage. The test substance was dispersed in corn oil (Sigma Chemical Company) and administered at a dosage of 5000 mg/kg. The animals were observed for clinical signs of toxicity at approximately 1-, 4- and 24-hours following administrations on the day of dosing and daily thereafter for 14-days. Body weights were recorded on Day-0, Day-7 and Day-14. All animals were subjected to a gross necropsy at study termination.
Result: One (1) animal died during the 14-day observation period. Clinical signs observed included decreased activity, decreased muscle tone, and diarrhea. No significant impairment on body weight gains were noted in either the male or female rats. Necropsy of the animal that died during the study revealed discolored kidneys, spleen, and liver. No visible lesions were observed in any of the animals at terminal necropsy. The estimated acute oral LD50 (combined sexes) for the test substance was determined to be > 5000 mg/kg.
Reliability: (1) valid without restriction
01-AUG-2000 (20)

5.1.2 Acute Inhalation Toxicity
-

5.1.3 Acute Dermal Toxicity

Type:	LD50
Species:	rabbit
Strain:	
Sex:	male/female
Number of Animals:	10
Vehicle:	other
Value:	> 2000 mg/kg bw
Method:	OECD Guide-line 402 "Acute dermal Toxicity"
Year:	1995 GLP: yes
Test substance:	other TS
Method:	Albino rabbits (five males and five females) were shaved in the caudal portion of the animals' trunks. One (1) day later, a 2000 mg/kg dose of 40 mesh test substance (obtained by grinding in motar/pestle) was placed onto the skin sites (approximately 10% of the body surface areas). The application sites were then covered with gauze, plastic, and elastic wraps and finally secured with non-irritating tape. After 24-hours of skin contact to the exposure areas, the gauze patches were removed and adhering test substance removed with moistened gauze. Skin test sites were scored for signs of erythema (redness) and edema (swelling) according to Draize procedures from Day-1 to Day-14 following cessation of exposures. Animals were observed for adverse clinical signs, mortality, and body weights (Day-0, Day-7, and Day-14). Necropsies were performed on the final day of observations (Day-14).
Remark:	A limit test
Result:	The test substance induced no deaths or apparent adverse clinical signs. Mild irritation (Grades 1,2 erythema; Grade 1 edema) was seen at skin sites of treated rabbits for periods ranging fron Day-1 to Day-10. Staining of skin was noted due to the dark color of the test substance. A body weight decrease was seen in one (1) of the ten (10) rabbits between Day-7 and Day-14. No compound-related non-dermal findings were observed in the study. No mortality or adverse clinical/necropsy changes were observed associated with the test substance. The dermal LD50 for the test substance was shown to be > 2000 mg/kg.
Test substance:	Tested as the commercial product
Reliability:	(1) valid without restriction

01-AUG-2000 (26)

5.1.4 Acute Toxicity, other Routes

-

5.4 Repeated Dose Toxicity

Species:	rat	Sex:	male/female
Strain:	Fischer 344		
Route of admin.:	oral feed		
Exposure period:	28 days		
Frequency of treatment:	Daily		
Post. obs. period:	2 weeks		
Doses:	0, 7.5, 30 and 120 mg/kg/day		
Control Group:	yes, concurrent vehicle		
NOAEL:	7.5 mg/kg		
LOAEL:	30 mg/kg		
Method:	other: Oral 4-week dietary study		
Year:	1996	GLP:	yes
Test substance:	as prescribed by 1.1 - 1.4		

Method: The test substance was prepared by grinding in a coffee mill, sieved through a 125 um mesh screen and mixed with rodent diet NIH-07 at 0, 120, 470, 1900 ppm (0, 7.5, 30, and 120 mg/kg/day). Stability, homogenity, and dose verification were performed to confirm compliance with protocol. The prepared dosed feed was presented to 14 male and 14 female rats (Fischer 344) per test group at twelve weeks of age for four (4) weeks. Six (6) rats/sex/group were held for post-exposure in two (2) week recovery groups. Test rats were monitored for body weights, feed consumption, and clinical signs. Collections were performed on six (6) or three (3) rats/sex/group at 28-days and 42-days sacrifice periods for blood (hematologies and clincal chemistries) and urinalyses, respectively. Necropsies were performed on all rats, and organs were weighed (liver,kidneys, pituitary, uteri, heart, brain, spleen, thryoids, adrenals, testes, and ovaries). These and other major organs were preserved in formalin, stained with H&E, and subjected to microscopic evaluations. Liver, kidney, and urinary bladder slices were subjected to immunohistochemical staining for proliferating cell nuclear antigen (PCNA) for assessment of cellular division.

Result: The test substance was shown to be completely stable in diets for 46-days. Mixing procedures produced homogeneous diets that were found within 10% of target concentrations. No compound-related deaths occurred, The boby weights were not affected in male rats whereas the high dose female rats displayed 5% body weight decreases during study weeks two (2) through four (4). Food consumption was decreased in the high dose males and in the mid- and high dose females mainly during study weeks two (2) through four (4). Various test substance-induced hematological changes occurred that included: increased mean corpuscular volumes and decreased mean corpuscular hemoglobin concentrations (high dose males and females) and blood bilirubin and cholesterol increases (high dose males and females). Most blood endpoints tended to approach control levels during week two (2) of the recovery

period. No dose-related urinary changes were seen. Organ

weight increases were seen at 28-days for liver and kidneys (high dose males and females; mid-dose females) and heart and spleen (high dose females). Only the kidney weights did not reach control levels by 42-days. There were no gross tissue or microscopic changes related to the test substance. Proliferating cell nuclear antigen (PCNA) exams showed cell division changes for: increases for liver cells (High dose males and females and mid-dose males at 28-days only); changes for kidney cells (decreases in high dose females at 28-days and increases in high dose males and females at 42-days; and increasing trend in urothelial cells in bladder (low and mid-dose males and females at 28-days). Macrocytic anemia was the primary change in rats related to the test substance administration. This change was reversible within 2 weeks following dietary exposure as were liver weight and serum cholesterol elevations. These changes were very minor, and had no apparent toxicological significance in this study. The lack of dose-responsiveness in the PCNA data provides results of uncertain importance to the assessment of the toxicity of this test substance.

Reliability: (1) valid without restriction
02-AUG-2000 (11)

Species: rat Sex: male/female
Strain: other: Fischer 344/N TacfBR
Route of admin.: gavage
Exposure period: 21 days
Frequency of treatment: Daily
Post. obs. period:
Doses: 0, 0.1, 0.3, 1.0, and 3.0 g/kg/bw
Control Group: yes, concurrent vehicle
LOAEL: 100 mg/kg bw
Method: other: Oral 3-Week Range-Finding Study
Year: 1994 GLP: yes
Test substance: as prescribed by 1.1 - 1.4
Remark: A 4-week diet-study was also conducted.
Result: Doses of 1.0 and 3.0 g/kg/day of WINGSTAY 100 administered by gavage for up to 6 days were lethal for male and female F344 rats. The only pertinent gross finding of all unscheduled deaths was the paleness of most external surfaces and viscera. The mid-low (0.3 g/kg/day) and low (0.1 g/kg/day) doses caused time and dose related significant body weight gain loss, liver weight increase and hepatocellular labeling index increase at 0.1 g/kg. Therefore, in the subchronic studies, the recommended daily dose of WINGSTAY 100 should not exceed 100 mg/kg/day, if administered by gavage.

Test substance: The test substance was prepared in an olive oil suspension for dosing
Reliability: (1) valid without restriction
02-AUG-2000 (5)

5.5 Genetic Toxicity 'in Vitro'

Type: Ames test
System of testing: Ames/E. coli preincubation; Salmonella typhimurium TA-98, 100, 1535, 1537, 1538, and WP2 uvrA
Concentration: Salmonell stains without S9 activation:0.167, 0.5, 1.67, 5, 16.7, and 50 ug/plate; Salmonella strains with S9 activation:1.67, 5, 16.7, 50, 167, and 500 ug/plate; E.coli with/without S9 activation:1.67, 5, 16.7, 50, 167, and 500 ug/plate
Cytotoxic Conc.:
Metabolic activation: with and without
Result: positive
Method: other: Japan's Industrial Safety & Health Law, a combination of OECD Guidelines 471 and 472.
Year: 1993 GLP: yes
Test substance: as prescribed by 1.1 - 1.4
Method: In a preliminary assay, revertant frequencies for all doses of the test substance in tester strains TA1535, TA1537, TA98, TA100, and WP2 uvrA with S9 metabolic activation, and in tester strains TA1535, TA1538, TA98, TA100 and WP2 uvrA without S9 activation, approximated the concurrent negative controls. However, statistically significant, increases in revertant frequencies, to approximately 1.7- to 2.5-fold control values, were observed in tester strain TA1538 with S9 metabolic activation and in tester strain TA1537 without S9 metabolic activiation. In addition, the increases observed in strain TA1538 with S9 metabolic activation were dose dependent.

In a confirmatory assay, revertant frequencies for all doses of the test substance in tester strains TA1535, TA100, and WP2 uvrA with metabolic activation, and in tester strains TA1535, TA1538, TA98, TA100, and WP2 uvrA without S9 metabolic activation, approximated control values. Statistically significant, dose-dependent increases in revertant frequencies, to control values, were observed in tester strains TA1537, TA1538, and TA98 with metabolic activation. Statistically significant increases in revertant frequencies, to control values, also were observed in tester strain TA98 without S9 metabolic activation. However, these latter increases apparently were not dose related.

The test substance was re-evaluated in all five Salmonella strains with S9 metabolic activation, and in tester strain TA98 without S9 metabolic activation. Revertant frequencies for all doses of the test substance in tester strains TA1535, TA1537, and TA100 with S9 metabolic activation, and in tester strain TA98 without S9 metabolic activation, approximated or were less than control values. Statistically significant, dose-dependent increases in revertant frequencies, to control values, were observed in tester strains TA1538 and TA98 with S9 metabolic activation. All

positive and negative control values in all assays were within acceptable limits.

Result: The test substance was shown to cause mutations in Ames/Salmonella strains TA1538 and TA98 with S9 activation.

Reliability: (1) valid without restriction

04-AUG-2000 (16)

Type: Ames test

System of testing: Ames/Salmonella-E.coli Liquid Pre-incubation Assay in Salmonella strains TA1535, TA1537, TA1538, TA98, and TA100 and in E.coli strain WP2 uvrA.

Concentration: Salmonella strains with S9: 1.67, 5, 16.7, 50, 167, and 500 ug/plate; Salmonella strains without S9: 0.167, 0.5, 1.67, 5, 16.7, and 50 ug/plate; E.coli with/without S9: 1.67, 5, 16.7, 50, 167, and 500 ug/ plate.

Cytotoxic Conc.:

Metabolic activation: with and without

Result: positive

Method: other: Japan's Industrial Safety & Health Law, a combination of OECD Guidelines 471 and 472.

Year: 1994 GLP: yes

Test substance: as prescribed by 1.1 - 1.4

Method: In a preliminary assay, revertant frequencies for all doses of the test substance in tester strains TA1535, TA1537, TA100, and WP2 uvrA with and without S9 metabolic activation approximated the concurrent negative controls. However, statistically significant, increases in revertant frequencies, to control values, were observed in tester strains TA1538 and TA98 with S9 metabolic activation. In addition, the increases observed in strain TA1538 with S9 metabolic activation were dose dependent.

In a confirmatory assay, revertant frequencies for all doses of the test substance in tester strains TA1535, TA100, and WP2 uvrA with metabolic activation, and in tester strains TA1535, TA1537, TA1538, TA100, and WP2 uvrA without S9 metabolic activation, approximated control values.

Statistically significant, dose-dependent increases in revertant frequencies,to control values, were observed in tester strains TA1537, TA1538, and TA98 with metabolic activation. Statistically significant increases in revertant frequencies, to control values, also were observed in tester strain TA98 without S9 metabolic activation. However, these latter increases apparently were not dose related.

The test substance was re-evaluated in all five Salmonella strains with S9 metabolic activation, and in tester strain TA98 without S9 metabolic activation. Revertant frequencies for all doses of the test substance in tester strains TA1535, and TA100 with S9 metabolic activation, and in tester strain TA98 without S9 metabolic activation, approximated control values. Statistically significant, dose-dependent increases in revertant frequencies, to

control values, were observed in tester strains TA1537, TA1538, and TA98 with S9 metabolic activation. All positive and negative control values in all assays were within acceptable limits.

Result: The test substance was shown to cause mutations in Ames/Salmonella strains TA1537, TA1538 and TA98 with S9 metabolic activation.

Reliability: (1) valid without restriction

04-AUG-2000 (17)

Type: Cytogenetic assay

System of testing: Chromosomal aberration assay in CHO cells

Concentration: 0.4, 2, 4, and 25 ug/mL

Cytotoxic Conc.:

Metabolic activation: with and without

Result: negative

Method: OECD Guide-line 473 "Genetic Toxicology: In vitro Mammalian Cytogenetic Test"

Year: 1993 GLP: yes

Test substance: as prescribed by 1.1 - 1.4

Method: In the structural Chromosomal Aberration assay, duplicate cultures were established for each dose level. Three treatment schedules were used: a) First set of cultures were treated for 5-hours with the appropriate dose of the test sample in Ham's F12 serum free (F12SF) medium either in the presence or absence of S9 metabolic activation along with concurrent negative and positive controls followed by three (3) Puck's saline washes and medium replacement; b) Second set of cultures were treated for 24-hours with the test substance or control articles in Ham's F12 medium containing five (5) % serum (F12FCM5%) without S9 metabolic activation, and; c) Third set of cultures were treated for 48-hours with

the test substance or control articles in F12FCM5% medium without S9 metabolic activation. Two (2) to three (3) hours prior to harvest, Colcemid (2X10-7M) was added to all sets of cell cultures to arrest dividing cells in metaphase. CHO cells were harvested at the eppropriate time and metaphase slides were prepared and stained.

The data from one hundred metaphases from each culture (200 metaphases per dose point) were pooled for statistical analysis. Data were evaluated by using the chi-square of aberrant versus normal cells while comparing each dose level to its concurrent negative control. The data were also analyzed for statistical significance by pairwise t-tests comparing the number of aberrations per cell in each treated dose versus the negative control.

Result: Analysis of the data for the 24-hour treatment with the test substance indicated that there were statistically significant dose-related increases in the frequency of aberrations/cell and proportion of aberrant metaphases at doses 2 and 4 ug/mL. The data for the 2 and 4 ug/mL doses produced a statistically significant linear trend when

analyzed by the Cochran/Armitage Linear Trend Test. To verify the biological sighificance of this finding, the 24-hour treatment was repeated.

In the confirmatory assay, the test substance was re-evaluated at doses of 25 ug/mL with S9 metabloic activation (5-hour treatment) and 0.4, 2, and 4 ug/mL without S9 metabolic activation (24-hour treatment). Analysis of the data for the 5-hour treatment did not produce statistically significant increases in aberrations/cell or in proportion of aberrant metaphases.

Analysis of the data for the 24-hour treatment indicated a statistically significant increase in aberrations/metaphase at the mid-dose (2 ug/mL) with S9 metabolic activation but there were no significant increases in the proportion of aberrant metaphases. However, when the data for 2 ug/mL (0.045 + or - 0.208) were compared to the untreated control data (0.025 + or - 0.157) or to Pharmakon historical acetone data (0.034 + or - 0.021), there were no statistically significant increases in the frequency of aberrations/metaphase. Therefore, the positive finding in the t-test for 2 ug/mL was considered a statistically artifact with no biological significance. There were no other statistically significant increases in aberration/metaphase or in the proportion of aberrant metaphases at any of the remaining dose levels for the 24-hour treatment.

The test substance was judged negative (non-clastogenic) based on its inability to reproducibly induce dose-related increases in structural chromosomal aberrations in CHO cells.

Reliability: (1) valid without restriction

20-FEB-2001 (19)

Type: DNA damage and repair assay
System of testing: E. coli Pol A1- Liquid Suspension Assay
Concentration:
Cytotoxic Conc.:
Metabolic activation: without
Result: positive
Method: other
Year: 1980 GLP: no
Test substance: as prescribed by 1.1 - 1.4
Reliability: (2) valid with restrictions
Although the study was old and was not conducted to GLP, the test parameters were based on a scientifically sound procedure for that time period and the study was properly conducted.

04-AUG-2000 (32)

Type: other: Transformation Assay
System of testing: Balb/3T3 In Vitro Transformation Assay
Concentration: .01 ug/ml to 1.0 ug/ml
Cytotoxic Conc.:
Metabolic activation: without
Result: negative
Method: other
Year: 1981 GLP: no
Test substance: as prescribed by 1.1 - 1.4
Reliability: (2) valid with restrictions
Although this study was probably not conducted to GLP, the test parameters used were based on a known and well established procedure.

04-AUG-2000 (12)

Type: other: Unscheduled DNA Synthesis Assays (UDS) with Rat Hepatocytes
System of testing: Hepatocytes form male Fischer 344 (F344/Crl) rats
Concentration: Slightly above their limits of solubility
Cytotoxic Conc.:
Metabolic

activation: without
Result: negative
Method: other: Unscheduled DNA Synthesis Assays (UDS) with Rat Hepatocytes on Test substance Condensation Products
Year: 1999 GLP: yes
Test substance: other TS: Test substance condensation products with Dicylopentadiene
Method: The test substance, 1,4-Benzenediamine, N.N'-mixed Ph and tolyl. derivs., was reacted with Dicyclopentadiene in varying ratios, resulting in three condensation products. Each of these condensation products were subjected to independent in vitro unscheduled DNA synthesis (UDS) assays with hepatocytes form male Fischer 344 (F344/Crl) rats. All three (3) condensation products were tested at concentrations slightly above their limits of solubility in the tissue culture medium. Hepatocytes were exposed to test substances for 18-20 hours to allow bioactivation and DNA repair. The assay was based on the incorporation of 3H-thymidine into the hepatocyte's DNA during repair of DNA-damage. This incorporation was monitored by counting Net Nuclear Grains (NNG) formed on photographic emulsion placed on the cells adhering to glass slides. Criteria for a positive response included : (a) Significant increase in number of grains at two (2) levels of exposure above negative control levels, (b) A dose-responsiveness in grain counts up to toxic levels of exposure, and (c) At least one (1) value for NNG that is five (5) or above. A negative response is reported for NNG's that are <0, and an equivocal or inconclusive response are results that are 0<#<5.
Result: In all the Unscheduled DNA Synthesis Assay (UDS) trials, the three (3) negative controls {the untreated cells control, F,

and Dimethylsulfoxide (DMSO)} had negative values for Net Nuclear Gain (NNG) counts (<0). A positive control, 2-Aminofluorene (2-AF) was positive for induction of UDS; the mean NNG counts were 45.92 and 58.99 in the first and second assays, respectively, indicating assay validity. (i.e., hepatocytes were capable of metabolic activation and DNA repair). The positive control responses occurred at toxic levels. UDS assay results for NNGs were in the range of -26 to -46, demonstrating a lack of UDS activity for the three (3) condensation products at concentrations greater than their solubilites in the test media. The results indicated that, under controlled laboratory conditions, the condensation products from the reaction of 1.4-Benzenediamine, N,N', mixed Ph and tolyl. derivs. with Dicyclopentadiene were negative for induction of UDS in rat hepatocytes at concentrations up to and greater than their solubilities. This assay demonstrated a lack of genetic activity in this mammalian DNA-repair test system.
Reliability: (1) valid without restriction

07-AUG-2000 (36)

5.6 Genetic Toxicity 'in Vivo'

Type: Drosophila SLRL test
Species: Drosophila melanogaster Sex:
Strain:
Route of admin.: oral feed
Exposure period: 24 hours
Doses: 50 ug/ml and 10 ug/ml
Result: negative
Method: other: Drosophila melanogaster (Fruit Fly) System
Year: 1979 GLP: no
Test substance: as prescribed by 1.1 - 1.4
Result: Negative under conditions of the assay
Reliability: (2) valid with restrictions
Although the study was old and was not conducted to GLP, the test parameters were based on a scientifically sound procedure for that time period and the study was properly conducted.
04-AUG-2000 (31)

Type: Drosophila SLRL test
Species: Drosophila melanogaster Sex:
Strain:
Route of admin.: oral feed
Exposure period: 24 hours
Doses: 0.05 mg/ml and 0.63 mg/ml
Result: negative
Method: other: Drosophilia SLRL Assay
Year: 1979 GLP: no
Test substance: as prescribed by 1.1 - 1.4
Result: Negative under conditions of the assay.
Reliability: (2) valid with restrictions
Although the study was old and was not conducted to GLP, the test parameters were based on a scientifically sound

procedure for that time period and the study was properly conducted.

04-AUG-2000 (13)

Type: Micronucleus assay
Species: mouse Sex: male/female
Strain: CD-1
Route of admin.: i.p.
Exposure period: single dosing
Doses: 0, 250, 1250, 2500 mg/kg test chemial; 0.5 g/kg TEM (+ control)
Result: negative
Method: OECD Guide-line 474 "Genetic Toxicology: Micronucleus Test"
Year: 1993 GLP: yes
Test substance: as prescribed by 1.1 - 1.4
Method: Nine (9) groups of mice (CD-1) were acclimated to laboratory conditions for 25-days prior to initiation of the study. THe mice were randomized by body weight and assigned to groups using a computer-generated random number list.

Each group of mice was comprised of ten (10) animals(five (5) males/five (5) females). Each mouse received a single intrperitoneal dose at 10 mL/kg of body weight. The test substance at dose levels of 250, 1250, anf 2500 mg/kg was adnimistered to three (3) groups of mice which were sacrificed at 24-, 48-, and 72-hours post dose. Concurrently, the negative control, Dimethylsulfoxide (DMSO)/corn oil, was administered, as dose volume of 10 mL/kg of body weight, to three (3) groups of mice. A group of these mice were included in each sampling time. The positive control, Triethylenemelamine at 0.5 mg/kg, was administered to one (1) group of mice and sacrificed at 24-hours post dose.

All mice were sacrificed and their femurs were removed. Their bone marrow was removed by flushing. Smears were made of the suspended cells.

One (1) thousand young erythrocytes were evaluated for a change of ratio of polychromatic erythrocytes (PCE) to normochromatic cells (NCE).

5. Toxicity

Result: There were no statistically significant depressions in the PCE/NCE ratios in any groups of mice except for the 2500 mg/kg group at 48-hours sacrifice time ($p<0.01$) which was an indication that the test substance had reached the bone marrow and was toxic to erythrocytes.

Analysis of the micronucleus data for the groups treated with the test substance indicated that there were no statistically significant increases in the frequency of

micronucleated PCEs. The test substance was judged negative (non-clastogenic) based on its inability to induce micronucleated PCEs.
Reliability: (1) valid without restriction
04-AUG-2000 (18)

Type: other: 32P Postlabeling Assay for Detection of Adduct Formation in Rat DNA
Species: rat Sex: male/female
Strain: other: Fischer 344/N TacfBR
Route of admin.: gavage
Exposure period: 7 days
Doses: 0., 0.3, 1.0, and 3.0 g/kg/bw
Result: negative
Method: other: 32P Post-Labeling Assay for DNA Adduct Formtion
Year: 1995 GLP: yes
Test substance: as prescribed by 1.1 - 1.4
Remark: The purpose of the study was to determine the potential of WINGSTAY 100 to bind covalently to liver and urinary bladder DNA of male and female rats after in vivo administration of WINGSTAY 100.
Result: Under conditions of the study, the test substance did not induce DNA-adducts in the liver and urinary bladder DNA of rats.
Reliability: (1) valid without restriction
07-AUG-2000 (4)

5.8 Toxicity to Reproduction

Type: Two generation study
Species: rat Sex: male/female

Strain: Sprague-Dawley
Route of admin.: oral feed
Exposure Period: F0 exposed during 10 weeks premating, 2 weeks of mating, 3 weeks (gestation), and through the weaning (21 day) period. F1 males and females exposed for 10 weeks prior to mating.
Frequency of treatment: Daily
Premating Exposure Period
male: 10 weeks
female: 10 weeks
Duration of test: 9 months
Doses: 0, 120, 400 or 1500 ppm.
Control Group: yes, concurrent no treatment
Method: OECD Guide-line 416 "Two-generation Reproduction Toxicity Study"
Year: 2000 GLP: yes
Test substance: as prescribed by 1.1 - 1.4
Method: This study was designed in compliance with EPA GLP and USEPA FIFRA guidelines. Dose levels were established from a rangefinding study at Research Triangle Institute which employed dietary levels of 120, 1900, and 5700 ppm of WINGSTAY 100. The top level was lethal to dams and offspring, 1900 ppm induced one nonviable litter in 9 total, and thus, the top dose for the definitive study was decreased by 20% to assure high viability in test group. No effects were seen at 120 ppm.

This study used 30 SpragueDawley rats/sex/dose (F0) exposed to diets containing 0, 120, 400 or 1500 ppm WINGSTAY 100 during 10 weeks premating, 2 weeks mating, 3 weeks (gestation), and through the weaning (21 day) period. F1 litters were culled to 10 each each at 4 days postnatal (PND) 30 other F1 males and females/group chosen for pairing, and fed WINGSTAY 100 as above for 10 weeks prior to mating. After mating/gestation of F1, the resulting F2 rats were delivered, and maintained through weaning period (to PND 21). Weekly body weights (BWs) and food consumption (FC), and daily clinical observations were recorded. Necropsies and histopathology (primary kidneys) were performed on selected rats from each sex/group/generation (all F0 and F1 dams at PND21, three F1 and F2 pups/test group at PND21). Remaining F1 and F2 rats were euthanized without examination. Data were collected on vaginal cytology, mating, pregnancy, litter, and pup parameters.
Remark: WINGSTAY 100 induced dystocia (difficult deliveries) in pregnant rats which may have led to prolonged gestation and increased perinatal deaths, decreased live births, and increased pup weights. In addition, polycystic lesions were observed at all dose levels. Prolonged gestation has previously been associated with the WINGSTAY component DPPD, and polycystic kidneys were observed in DPamine-treated

rats. Based upon adult toxicities, reproductive and offspring endpoints, there was no NOEL for WINGSTAY 100 in this study.

Result: High dose females had decreased Body Weights (BWs) relative to other test groups throughout majority of study period. Mortality during gestation/lacation were: F0 dams- 0 in 24 pregnancies, 0/27, 3/24, 4/25; F1- 0/22, 0/23, 1/22, 1/24. Numbers of pregnancies with no live births: F0- 0, 1, 1, 10; F1- 0, 1, 1, 2. Gestational length: F0- 22.2 days, 22.4 days, 22.8*, 23.5*; F1- 22.2, 22.8*, 23.1*, 23.2* (* = statistically sighnificant). The number of live pups/litter: F0-15.6, 14.1, 11.9, 7.6*; F1- 15.6, 13.7, 13.3, 10.8*. Pups weights (g) on PND 0: F0- 6.38, 6.79*, 6.93*, 6.63*; F1- 6.32, 6.89*, 6.99*, 6.63*. WINGSTAY 100-related kidney lesions were observed grossly (as white or clear cysts) and microscopically (polycyctic findings with variable severity): F0 adults- males 0/0, 0/0, 0/0, 0/1 and females 0/0, 0/0, 0/2, 3/9; F1 weanlings- males 0/23, 1/25, 8/20, 10/11 and females 0/22, 5/26, 7/18, 11/11; F1 adults- males 0/30, 5/30, 10/30, 21/30 and females 0/30, 2/30, 1/30, 18/30; F2 weanlings- males 0/60, 3/64, 6/19, 15/16 and females 0/60, 5/64, 8/19, 15/15. The severity of kidney lesions were also dose related.

Reliability: (1) valid without restriction

11-FEB-2001 (35)

5.9 Developmental Toxicity/Teratogenicity

Species: rat Sex: female
Strain: Sprague-Dawley
Route of admin.: gavage
Exposure period: 10 days
Frequency of treatment: Dosed on days 6-15 gestation
Duration of test:
Doses: 0, 20, 70, 200 mg test material in 5 ml corn oil/kg
Control Group: yes, concurrent vehicle
NOAEL Maternalt.: 70 mg/kg bw
NOAEL Teratogen.: <= 200 mg/kg bw
Method: OECD Guide-line 414 "Teratogenicity"
Year: 1995 GLP: yes
Test substance: other TS
Method: Preliminary trials in 8 rats/group indicated that 600 mg/kg was lethal to 50% of maternal rats while 200 mg.kg caused decreased body weights in materanl and fetal animals. There were no effects at 20 or 70 mg/kg. Consequently, 200 mg/kg was selected as the top (high) dose in the definitive study, Confirmation of the test dose solutions were confirmed analytically.

The definitive study used 25 inseminated female rats per test group (0, 20, 70, and 200 mg of test substance/kg doses in five (5) mL corn oil/kg). The animals were dosed on Days 6-15 gestation. Body weights, food consumption, liver

weights, clinical changes, pregnancy rates, and corpora lutea counts were followed along with numerous fetal parameters. All fetuses were weighed, sexed, and assessed for external and visceral abnormalities. One (1) half of the fetuses were examined for skeletal abnormalities while the second half were subjected to cranial bone assessments.

Remark: Administered in 5 ml corn oil/kg by gavage

Result: The test substance induced no lethality. Deficits were seen in maternal body weights (Day-12 and body weight change from Day-6 to Day-15) and food consumption (during treatment period) at the highest dose only (200 mg/kg). Pregancy rates, litter sizes, number of live fetuses, uterine implantation, and all gestational parameters were unaffected by chemical treatment. There was a linear trend towards lower body weights in fetuses with increasing doses (approximately 5% decrease in 200 mg/kg group). Assessment of cranial, skeletal, visceral, and external appearance discerned no compound-related abnormalities (malformatiuons or variations) according to established criteria. The test material produced minimal effects (body weight) to maternal rats from oral dosing of 200 mg/kg during pregnancy. There was no induction by the test chemical of birth defects (major or minor) in fetal animals.

Test substance: Tested as the commercial product

Reliability: (1) valid without restriction

08-AUG-2000 (21)

Species: rat Sex: male/female

Strain: Sprague-Dawley

Route of admin.: oral feed

Exposure period: Varied, see method

Frequency of treatment: Varied, see method

Duration of test:

Doses: 2500 ppm

Control Group: yes, concurrent vehicle

Method: other: Mechanistic Study

Year: 2000 GLP: no

Test substance: as prescribed by 1.1 - 1.4

Method: The toxicity of the test substance to maternal and 1st. generation offspring was evaluated by exposing CD (Sprague-Dawley) rats to fixed dietary concentrations of 2500 ppm during different time periods (i.e. exposures during prebreed, mating, gestation, and/or lactation). Five (5) Groups (20/sex/Group) were studied including: Group one (1)- Negative control; Group two (2)- Dietary test substance during prebreed and mating, exposures ended on gestation day (gd)-0; Group three (3)- Dietary test substance during gestation and lactation, exposures began on gd-0; Group four (4)- Dietary test substance during prebreed, mating, gestation, and lactation, the Positive control and; Group

five (5)- Dietary test substance during prebreed, mating, gestation, and lactation, plus 600 ppm of iron gluconate in the drinking water for prebreed through lactation.

5. Toxicity

Males and females were paired within Groups (1:1) for the two-week mating period. Once a given female was found to be sperm positive {date designated as gestation day (gd)-0}, "her" male was euthanized and discarded. On the day of delivery (pnd-0), pups were counted, sexed, and weighed. On pnd-4, litters were culled to ten, counted, sexed, and weighed. On pnd-7, -14, and -21, pups were counted, sexed, and weighed. All pups were euthanized and one (1)/sex/litter necropsied on pnd-21. Dead pups on pnd-0 and -1 were examined macroscopically (necropsied) for polycystic kidneys. Female body weights and feed consumption were recorded weekly during prebreed, gestation, and postnatally. At necropsy on pnd-21, the maternal spleen, liver, and kidneys were weighed and retained in a fixative. Kidneys form Groups one (1) and five (5) were examined histopathologically. Blood sampling was performed on gestation day-21 and pnd-21 from all females (pregnant) by tail vein withdrawal. Blood sampling was performed on pnd-21 on the F1 offspring by withdrawal from the abdominal vena cava at sacrifice. The blood parameters assessed were: WBC, RBC, Hgb, Hct, MCV, MCH, MCHC, RDW, Platelets, WBC Diffential (to correct the RBC and WBC counts for Nucleated Red Blood Cells) and Methemoglobin. On gd-21, a second sample of blood was taken via tail vein from all pregnant females in all Groups, with plasma frozen for possible subsequent analysis for specific hormones. For Group three (3), any female who had not yet delivered by gestation day-23 had blood taken from the tail vein and plasma frozen. On pnd-21, the spleen, liver, kidneys, and heart from one (1) pup/sex/litter were weighed and retained in a fixative. The kidneys from all offspring were examined histologically. Statistical analysis included both parametric and nonparametric tests for continuous and discrete data.

Remark: The objectives of this study were to confirm and further characterize prviously-observed effects following the test substance administration to pregnant rats. This study was designed (1) to determine the necessary and sufficient timing of exposure to maternal females at a fixed dietary concentration of the test substance to produce dystocia, prolonged gestation, and polycystic kidneys in offspring, (2) to determine whether the test substance results in demonstratable macrocytic anemia in maternal animals, (3) to determine if there is treatment-induced anemia and whether iron supplementation ameliorates or prevents the anemia, dystocia, and/or polycystic kidneys, and (4) to determine if F0 parental females exhibit polycystic kidneys due to

dietary exposure to the test substance.

Result: F0 Males: The test substance intake over the prebreed period (Study Days 0-28) averaged 180 mg/kg/day for all three (3) exposed Groups {two (2), four (4), and five (5)}. Iron gluconate intake in Group five (5) averaged 56 mg/kg/day (Study Days-0 to 28). Clinical observations were found to be unrelated to compound administration.

F0 Females: The test substance intake averaged 187-192

mg/kg/day for Groups two (2), four (4) and five (5) during gestation days (gd)-0 to 28. Iron gluconate intake during gestational days-0 to 28 in Group five (5) averaged 53 mg/kg/day. Clinical observations during gestation included one (1) female found dead in Groups three (3) and four (4), alopecia predominantly in Groups four (4) and five (5), pale eyes and tail, pale (not otherwise specified) almost exclusively in Groups three(3), four (4) and five (5) (all exposed), pilorection in Groups three (3), four (4) and five (5), and delayed parturition in Groups three (3), four (4), and five (5). The hematological profile of maternal rats on gestation day-21 found no evidence on macrocytic anemia in any groups.

REPRODUCTIVE/DEVELOPMENTAL: Gestational index (a measure of live litters relative to pregnant females) was significantly increased in Groups three (3) and four (4) but not in Group five (5). Male mating, fertility, and pregnancy indices were equivalent across all groups. Gestational length in days was significantly prolonged in Group three (3) (23.6+/-0.2), Group four (4) (23.8+/-0.2), and Group five (5) (23.5+/-0.2) relative to Control Group value (22.2+/-0.1) and the value in Group two (2) (22.3+/-0.1). Number of implantation sites per litter was significantly reduced in Group five (5). Percent of postimplantation loss was significantly increased in Groups three (3) and four (4). Pups per litter were significantly reduced in Groups three (3), four (4) and five (5), and number of dead pups per litter were significantly increased in Groups three (3) and four (4). Weanling gross and microscopic findings were limited to hydronephrosis in Groups one (1) and two (2), gas in intestines in Group two (2), and gross evidence of polycystic kidneys in Groups three (3), four (4), and five (5). Maternal hematologic profiles at sacrifice (21 days after delivery) indicated statistically significant changes in most erythrocyte parameters. The white blood cell differential counts indicated changes (as percent of cells examined) as follows: increase in segmented neutrophils and decrease in lymphocytes only in Group four (4), with no treatment-related changes in the percentages of monocytes or eosinophils. Histopathologic assessment was performed on

kidneys of all maternal rats in Groups one (1) and five (5). Polycystic kidneys were observed microscopically (but not macroscopically) in three (3) of 20 animals in Group five (5), with no polycystic kidneys observed in Group one (1).

The timing of exposure to the test substance with respect to pregnancy is an important determinant of toxicity. Exposure of F0 females to 2500 ppm of the test material during gestation is necessary and sufficient to produce dystocia (prolonged gestation). It is necessary and sufficient to expose F0 dams during gestation and/or lactation to produce polycystic kidneys in the F1 offspring. Since no Groups were exposed only during gestation or only during lactation, it is not possible to further define how exposure timing

affects this endpoint. There was no demonstratable macrocytic anemia in gestation day-21 (gd-21) F0 dams in any treatment Group, but at post delivery day-21 (pnd-21), F0 mothers exposed prior to and during mating, gestation, and lactation were anemic. The F1 offspring at pnd-21 did not consistently display evidence of macrocytic anemia. Iron supplementation did not affect pnd-21 maternal anemia, dystocia, or incidence/severity of polycystic kidneys in the F1 offspring. However, perinatal survival of the offspring was affected. Microscopic, but not macroscopic evidence of polycystic kidneys was found in 15 percent of dams treated prior to and during mating, gestation, and lactation (with iron supplementation). Controls had neither macroscopic nor microscopic indications of polycystic kidneys. Exposure of animals to the test substance prior to and during mating {Group two (2)} did not appear to result in adverse affects to offspring. Furthermore, exposure during the prebreed/mating periods did not increase the affects produced from gestation/lactation exposures only.

Reliability: (2) valid with restrictions
Although this study was not conducted to GLP, the test parameters used were based on a sound scientific design.

09-AUG-2000 (15)

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(5) American Health Foundation, Preliminary Oral 3-Week Range-Finding Study for Administration of WINGSTAY 100 and R-59 in Male and Female Fischer 344 Rats, AHF Study R-1626 to The Goodyear Tire & Rubber Company, 1994.

(6) Bayer AG Data

(7) Bayer AG, Report No. 19778, December 10, 1990.

(9) Bayer AG, Unpublished Data, July 2, 1992

(11) Four-Week Dietary Study of WINGSTAY 100 in Fischer 344 Rats, Report # AHF R1664, American Health Foundation, 1/31/96

(12) Litton Bionetics, Inc., Balb/3T3 In Vitro Transformation Assay of NAILAX, Genetics Assay No.5419 to The Goodyear Tire & Rubber Company, 1981.

(13) Litton Bionetics, Inc., Drosophilia SLRL Assay with Nailax to The Goodyear Tire & Rubber Company, 1979.

(15) Mechanistic Study of Wingstay 100, Report Study # RTI 65C-6429-500, Research Triangle Park, February 11, 2000

(16) Pharmakon USA, Report # Ph301-GY-001-93 to The Goodyear Tire & Rubber Company, 1993

(17) Pharmakon USA, Report # Ph301-GY-004-93 to The Goodyear Tire & Rubber Company, 1994

(18) Pharmakon USA, Report # Ph309-GY-001-93 to The Goodyear Tire & Rubber Company, 1993.

(19) Pharmakon USA, Report # Ph320-GY-001-93 to The Goodyear Tire & Rubber Company, 1993.

(20) Pharmakon USA, Report # Ph402-GY-001-93 to The Goodyear Tire & Rubber Company, 1993.

(21) Reseach Triangle Research, Developmental Toxicity Evaluation of WINGSTAY 100 Administered by Gavage to CD (Sprague-Dawley) Rats, Report # 65C-5962-100/200 to The Goodyear Tire & Rubber Company, July 11, 1995.

(22) Ricerca, Inc., Biodegradation Study of a Rubber Antioxidant, Document Number 6011-94-0037-BC-001 to The Goodyear Tire & Rubber Company, 1994

(26) Springborn Laboratories, An Acute Toxicity Study in Rabbits with WINGSTAY 100 (Limit Test), Report # S94-001-3097.29 to The Goodyear Tire & Rubber Company, August 24, 1995.

(27) Springborn Laboratories, WINGSTAY 100-Acute Toxicity to Daphnids Under Flow-Through Conditions, Report # 96-1-6328 to The Goodyear Tire & Rubber Company, June 26, 1996.

(28) Springborn Laboratories, WINGSTAY 100-Determination of n-Octanol/Water Partition Coefficient, Report # 95-9-6103 to The Goodyear Tire & Rubber Company, December 12, 1995

(29) Springborn Laboratories, WINGSTAY 100-Prolonged (14-day) Acute Toxicity to Common Carp Under Flow-Through Conditions, Report # 96-2-6362 to The Goodyear Tire & Rubber Company, June 28, 1996

(30) Springborn Laboratories, WINGSTAY 100-Toxicity to the Freshwater Green Alga, Report # 96-4-6454 to The Goodyear Tire & Rubber Company, July 2, 1996.

(31) The Goodyear Tire & Rubber Company, Biological Effects of Nailax B in a Drosophilia melanogaster (Fruit Fly) Test System, 1979.

(32) The Goodyear Tire & Rubber Company, DNA Damage by WINGSTAY

100 Lot 48-3012 in the E. coli Pol A1- Assay, 1980.

(34) The Goodyear Tire & Rubber Company, WINGSTAY 100, Material Safety Data Sheet, 1993

(35) Two-Generation Reproductive Toxicity Evaluation of WINGSTAY 100 Administered in the Feed to CD (Sprague-Dawley) Rats, Report #: 65C-6429-400/200, Research Triangle Institute, 12/8/00.

(36) Unscheduled DNA Synthesis Assays (UDS) with Rat Hepatocytes on Wingstay 100 Condensation Products RWC-7703, RWX-7704, and RWC-7706, American Health Foundation, December 20, 1999

(37) WINGSTAY 100-Prolonged (14-Day) Acute Toxicity to Rainbow Trout (Oncorhynchus mykiss) Under Flow-through Conditions, Report # 96-11-6700, Springborn Laboratories, 2/21/97.

101-72-4
p-Phenylenediamine, N-Isopropyl-N'-Phenyl-

2. PHYSICAL-CHEMICAL DATA

*2.1 MELTING POINT

Value:	75-80 °C
Decomposition:	Yes **[ ]** No **[X]** Ambiguous **[ ]**
Sublimation:	Yes **[ ]** No **[X]** Ambiguous **[ ]**
Method:	FF83.9-1 Initial and Final Melting Point of Organic Compounds 1996
GLP:	Yes **[X]** No **[ ]** ? **[ ]**
Remarks:	Capillary Method
Reference:	ASTM D-1519 / Flexsys Physical Methods of Analysis

*2.2 BOILING POINT

Value:	161 °C
Pressure:	at 1 mm Hg
Decomposition:	Yes **[ ]** No **[X]** Ambiguous **[ ]**
Method:	Not listed
GLP:	Yes **[ ]** No **[ ]** ? **[X]**
Remarks:	
Reference:	Monsanto Toxicology Profile of Santoflex IP, 1990

†2.3 DENSITY (relative density)

Type:	Bulk density **[ ]**; Density **[X]**; Relative Density **[ ]**
Value:	1.180
Temperature:	20 °C
Method:	FF97.8-1 Flexsys Standard Method 1997
GLP:	Yes **[X]** No **[ ]** ? **[ ]**
Remarks:	Density of solids by displacement
Reference:	Flexsys Physical Methods of Analysis

*2.4 VAPOUR PRESSURE

Value:	0.00343 mm Hg
Temperature:	90 °C
Method:	calculated **[ ]**; measured **[X]** Not listed
GLP:	Yes **[ ]** No **[ ]** ? **[X]**
Remarks:	
Reference:	Monsanto Toxicology Profile of Santoflex IP, 1990

*2.5 PARTITION COEFFICIENT $\log_{10}P_{ow}$

Log Pow:	3.28 Log P
Temperature:	Not Determined
Method:	calculated **[X]**; measured **[ ]** SRC LogKow (KowWin) Program 1995
GLP:	Yes **[ ]** No **[X]** ? **[ ]**
Remarks:	
Reference:	Meylan, W.M. and. P.H. Howard, 1995 J. Pharm. Sci. 84: 83-92

***2.6 WATER SOLUBILITY**

A. Solubility

Value:	15 ppm
Temperature:	25 °C
Description:	Miscible **[ ]**; Of very high solubility **[ ]**; Of high solubility **[ ]**; Soluble **[ ]**; Slightly soluble **[ ]**; Of low solubility **[ ]**; Of very low solubility **[X]**; Not soluble **[ ]**
Method:	Saturated Solution / Solvent Extraction / GC.Analysis
GLP:	Yes **[ ]** No **[ ]** ? **[X]**
Remarks:	CH2Cl2 solvent, 100% recovery at 1 ppm. Equilibrated w/out light.
Reference:	Monsanto ES-78-SS-20, Environmental Sciences, 1978

B. pH Value, pKa Value

pH Value:	Not Applicable
pKa value	5.1 at 25°C
Method:	Estimated
GLP:	Yes **[ ]** No **[ ]** ? **[X]**
Remarks:	Value indicates that this compound will exist only slightly in the cation form
Reference:	HSDB database 101-72-4, SRC, University of Georgia SPARC SPARC On-Line Calculator

2.11 OXIDISING PROPERTIES

Results:	Maximum burning rate equal or higher than reference mixture**[ ]**; Vigorous reaction in preliminary test **[ ]**; No oxidising properties **[ ]**; Other **[ ]**
Method:	
GLP:	Yes **[ ]** No **[ ]** ? **[ ]**
Remarks:	
Reference:	

†2.12 OXIDATION: REDUCTION POTENTIAL

Value:	. . . . . mV
Method:	
GLP:	Yes **[ ]** No **[ ]** ? **[ ]**
Remarks:	
Reference:	

2.13 ADDITIONAL DATA

A. Partition co-efficient between soil/sediment and water (Kd)

Value:	
Method:	
GLP:	Yes **[ ]** No **[ ]** ? **[ ]**
Remarks:	
Reference:	

B. Other data

Results:	Henry's Law Constant = 1.4 x 10(-9) atm-cu m/mole

Remarks: Fragment Constant Estimation method. Volitazation from moist soil surfaces is not expected to be an important fate process.
Reference: HSDB – Lyman, W.J. et. al. Handbook of Chemical Property Estimation Methods, 1990

3. ENVIRONMENTAL FATE AND PATHWAYS

*3.1.1 PHOTODEGRADATION

Type: Air **[X]**; Water **[ ]**; Soil **[ ]**; Other **[ ]**
Light source: Sunlight **[ ]**; Xenon lamp **[ ]**; Other **[ ]**
Light spectrum: . . . . . nm
Relative intensity: . . . . . *(based on intensity of sunlight)*
Spectrum of substance: . . . . . nm
Concentration of Substance: . . . . . .
Temperature: . . . . . °C
Direct photolysis:
Half life: . . . . . .
Degradation: . . . . . % (weight/weight) after . . . . . (exposure time)
Quantum yield: . . . . . .
Indirect Photolysis:
Type of sensitizer: . . . . . .OH . . .
Concentration of sensitizer: . . 1560000 . . molecule/. cm^3 . . . . .
Rate constant (radical): . . . 218.3766 E-12. . . cm^3/molecule*sec
Degradation: . . . 50% at 0.588 Hrs . . . . . .
Method: calculated **[X]**; AOP Program (v1.89)
measured **[ ]**
GLP: Yes **[ ]** No **[X]** ? **[ ]**
Test substance: . molecular structure. . . . . , purity:. . . . . .
Remarks:
Reliability: (2) valid with restrictions
Accepted calculation method
Reference: Meylan W. and Howard P. (1999) EPIWin Modeling Program. Syracuse Research Corporation. Environmental Science Center, 6225 Running Ridge Road, North Syracuse, NY 13212-2510.

*3.1.2 STABILITY IN WATER

Type: Abiotic (hydrolysis) **[X]**; biotic (sediment)**[ ]**
Half life: Not Determined
Degradation: 99% at pH 7.0 at 25 °C after 24 Hours
Method: Phase I Hydrolysis Study / ID of Hydrolysis Products
GLP: Yes **[X]** No **[ ]** ? **[ ]** **Klimisch 1**
Test substance: Santoflex IP purple solid Lot # ND02-740, purity: >95%
Remarks: Rapid hydrolysis to benzoquinoneimine-N-phenyl and 4-hydroxy-diphenylamine. No starting material was detected by GC analysis after 7 days.
Reference: Monsanto ABC-32301, Analytical Bio-Chemistry Labs, 1986

*3.2 MONITORING DATA (ENVIRONMENTAL)

Type of Measurement: Background **[ ]**; At contaminated site **[ ]**; Other **[ ]**
Media:

Results:
Remarks:
Reference:

3.3 TRANSPORT AND DISTRIBUTION BETWEEN ENVIRONMENTAL COMPARTMENTS INCLUDING ESTIMATED ENVIRONMENTAL CONCENTRATIONS AND DISTRIBUTION PATHWAYS

***3.3.1 TRANSPORT**

Type: Adsorption **[ ]**; Desorption **[ ]**; Volatility **[ ]**; Other **[ ]**
Media:
Method:
Results:
Remarks:
Reference:

***3.3.2 THEORETICAL DISTRIBUTION (FUGACITY CALCULATION)**

Media: Air-biota **[ ]**; Air-biota-sediment-soil-water **[ ]**; Soil-biota **[ ]**; Water-air **[ ]**; Water-biota **[ ]**; Water-soil **[ ]**; Other **[ ]**

Method: Fugacity level I **[ ]**; Fugacity level II **[ ]**; Fugacity level III **[X]**; Fugacity level IV **[ ]**; Other (calculation) **[ ]**; Other (measurement)**[ ]**

Results:

	Concentration (percent)	Half-Life (hr)	Emissions (kg/hr)	Fugacity (atm)
Air	0.0158	1.18	1000	4.69e-013
Water	22.4	900	1000	1.97e-014
Soil	76.9	900	1000	3.94e-014
Sediment	0.68	3.6e+003	0	1.51e-014

	Reaction (kg/hr)	Advection (kg/hr)	Reaction (percent)	Advection (percent)
Air	257	4.36	8.57	0.145
Water	1478	620	15.9	20.7
Soil	1.64e+003	0	54.6	0
Sediment	3.62	0.376	0.121	0.0125

Persistence Time: 922 hr
Reaction Time: 1.16e+003 hr
Advection Time: 4.42e+003 hr
Percent Reacted: 79.2
Percent Advected: 20.8

Remarks:
Reliability: (2) valid with restrictions
Accepted calculation method
Reference: Meylan W. and Howard P. (1999) EPIWin Modeling Program. Syracuse Research Corporation. Environmental Science Center, 6225 Running Ridge Road, North Syracuse, NY 13212-2510.

***3.5 BIODEGRADATION**

Type: aerobic **[X]**; anaerobic **[ ]**
Inoculum: adapted **[X]**; non-adapted **[ ]**;
Concentration of the chemical: 1002 ug/l. related to COD **[]**; DOC **[]**; test substance**[X]**
Medium: water **[X];** water-sediment **[ ];** soil **[ ];** sewage treatment **[ ]**
Degradation: 50% after 2.5 Hours
90 % after 3.5 Hours

98% after 22 Hours

Results: readily biodeg. **[X];** inherently biodeg. **[ ]**; under test condition no biodegradation observed **[ ]**, other **[ ]**

Method: Natural Water Die-Away Test, Dixon, Hicks and Michael, 1981

GLP: Yes **[X]** No **[ ]** ? **[ ]** **Klimisch 1**

Test substance: Santoflex IP purple solid Lot# N76-7433, purity:>95%.

Remarks: Tests run in Mississippi River Water and purified water. The short half-lives in both systems suggest that the compound should not persist in natural aquatic environments.

Reference: Monsanto ES-81-SS-53, MIC Environmental Sciences, 1981

4. ECOTOXICITY

*4.1 ACUTE/PROLONGED TOXICITY TO FISH

Type of test: static **[X]**; semi-static **[ ]**; flow-through **[ ]**; other*)* **[ ]**
open-system **[ ]**; closed-system **[X]**

Species: Salmo gairdneri (Rainbow Trout)

Exposure period: 96 Hours

Results: LC_{50} (24h) = 0.62 mg/l
LC_{50} (48h) = 0.38 mg/l
LC_{50} (72h) = Not reported
LC_{50} (96h) = 0.34 mg/l
NOEC = 0.18 mg/l
LOEC = 0.24 mg/l

Analytical monitoring: Yes **[X]** No **[ ]** ? **[ ]**

Method: EPA Methods for Acute Toxicity Tests with Fish, Macroinvertebrates and Amphibians (1975)

GLP: Yes **[ ]** No **[ ]** ? **[X]** **Klimisch 2**

Test substance: Santoflex IP dark solid, Lot#NO12-002, purity: >95%

Remarks: Stock solutions prepared in reagent-grade acetone. Water quality parameters of temperature, dissolved oxygen and pH monitored throughout test. Observations and mortality counts were made every 24 hours.

Reference: Monsanto BN-76-255, EG&G Bionomics, 1977

Type of test: static **[X]**; semi-static **[ ]**; flow-through **[ ]**; other*)* **[ ]**
open-system **[ ]**; closed-system **[X]**

Species: Lepomis machrochirus (Bluegill Sunfish)

Exposure period: 96 Hours

Results: LC_{50} (24h) = 0.48 mg/l
LC_{50} (48h) = 0.43 mg/l
LC_{50} (72h) = Not reported
LC_{50} (96h) = 0.43 mg/l
NOEC = 0.24 mg/l
LOEC = 0.32 mg/l

Analytical monitoring: Yes **[X]** No **[ ]** ? **[ ]**

Method: EPA Methods for Acute Toxicity Tests with Fish, Macroinvertebrates and Amphibians (1975)

GLP: Yes **[ ]** No **[ ]** ? **[X]** **Klimisch 2**

Test substance: Santoflex IP dark solid, Lot# NO12-002, purity: >95%

Remarks: Stock solutions prepared in reagent-grade acetone. Water quality parameters of temperature, dissolved oxygen and pH monitored

	throughout test. Observations and mortality counts were made every 24 hours
Reference:	Monsanto BN-76-255, EG&G Bionomics, 1977

Type of test:	static **[ ]**; semi-static **[ ]**; flow-through **[X]**; other **[ ]** open-system **[ ]**; closed-system **[X]**
Species:	Pimephales promelas (Fathead Minnows)
Exposure period:	14 days
Results:	LC_{50} (24h) = 1.80 mg/l LC_{50} (192h) = 0.28 mg/l LC_{50} (240h) = 0.21 mg/l LC_{50} (336h) = 0.09 mg/l
Analytical monitoring:	Yes **[X]** No **[ ]** ? **[ ]**
Method:	EPA Methods for Acute Toxicity Tests with Fish, Macroinvertebrates and Amphibians (1975)
GLP:	Yes **[X]** No **[ ]** ? **[ ]** **Klimisch 1**
Test substance:	Santoflex IP dark solid rec'd 4/25/78, purity: >95%
Remarks:	Stock solutions prepared in reagent-grade acetone. Water quality parameters of temperature, dissolved oxygen, ammonia and pH monitored throughout test. Although the goal of the study was to determine a lethal threshold concentration of the test substance, the results indicated that this was not reached at 14 days. In addition, the test substance appeared to exhibit cumulative toxicity to the fish under test conditions.
Reference:	Monsanto AB78-120B, Analytical Bio-Chemistry Labs, 1979

Type of test:	static **[X]**; semi-static **[ ]**; flow-through **[ ]**; other) **[ ]** open-system **[ ]**; closed-system **[X]**
Species:	Paratanytarsus parthenogenetica (Midge)
Exposure period:	48 Hours
Results:	LC_{50} (24h) = 29 mg/l LC_{50} (48h) = 23 mg/l NOEC = Not Observed LOEC = 10 mg/l (lowest concentration tested)
Analytical monitoring:	Yes **[X]** No **[ ]** ? **[ ]**
Method:	EPA Methods for Acute Toxicity Tests with Fish, Macroinvertebrates and Amphibians (1975) and Gettings and Adams, Method for Conducting Acute Toxicity Tests with Midge 1980
GLP:	Yes **[X]** No **[ ]** ? **[ ]** **Klimisch 1**
Test substance:	Santoflex IP #1803025-C), purity: >95%
Remarks:	Stock solutions prepared in reagent-grade acetone. Water quality parameters of temperature, dissolved oxygen, ammonia and pH monitored throughout test.
Reference:	Monsanto 9AB981013, Analytical Bio-Chemistry Labs, 1981

4.2 ACUTE TOXICITY TO AQUATIC INVERTEBRATES

*A. Daphnia

Type of test:	static **[X]**; semi-static **[ ]**; flow-through **[ ]**; other **[ ]**; open-system **[ ]**; closed-system **[X]**

Species: Daphnia magna
Exposure period: 48 Hours
Results: EC_{50} (24h) = 2.8 mg/l
EC_{50} (48h) = 1.1 mg/l
NOEC = 0.56 mg/l
Analytical monitoring: Yes **[X]** No **[ ]** ? **[ ]**
Method: EPA Methods for Acute Toxicity Tests with Fish, Macroinvertebrates and Amphibians (1975)
GLP: Yes **[ ]** No **[ ]** ? **[X]** **Klimisch 2**
Test substance: Santoflex IP purple flakes Lot #676-7433, purity: >95%
Remarks: Acetone used to prepare stock solutions. Initial range-finding experiment run to determine appropriate concentrations for final experiment. Water quality parameters of dissolved oxygen, pH, hardness, temperature and alkalinity monitored throughout the test.
Reference: Monsanto AB-78-120, Analytical Bio-Chemistry Labs, 1978

***4.3 TOXICITY TO AQUATIC PLANTS, e.g. algae**

Species: Selanastrum capricurnutum (Freshwater alga)
Endpoint: Biomass **[ ]**; Growth rate **[X]**; Other **[ ]**
Exposure period: 96 Hours
Results: EC_{50} (96h) = 0.4 ppm for a chlorophyll, 0.5 ppm for cell numbers
NOEC = <0.1 ppm
LOEC = Not Determined
Analytical monitoring: Yes **[X]** No **[ ]** ? **[ ]**
Method: US EPA Algal Test Procedure: Bottle Test, 1971

open-system **[ ]**; closed-system **[X]**
GLP: Yes **[ ]** No **[ ]** ? **[X]** **Klimisch 2**
Test substance: Santoflex IP #BN-78-1384325, purity: >95%
Remarks: Both a chlorophyll and cell numbers measured to confirm results. Stock solutions prepared in acetone; acetone also used as solvent control Concentrations of test article determined by preliminary range-finding experiment.
Reference: Monsanto BN-78-1384325, EG&G Bionomics, 1978

5. TOXICITY

*5.1 ACUTE TOXICITY

5.1.1 ACUTE ORAL TOXICITY

Type: LD_0 **[ ]**; LD_{100} **[ ]**; LD_{50} **[X]**; LDL_0 **[ ]**; Other **[ ]**
Species/strain: Sprague-Dawley Albino Rats
Value: 900 mg/kg b.w.:
Discriminating dose: 1000 mg/kg/bw
Method: Defined Lethal Dose
GLP: Yes **[ ]** No **[ ]** ? **[X]** **Klimisch 2**
Test substance: Santoflex IP Lot# NO12-002, purity: <95%
Remarks: The test article was administered to groups of male and female rats by oral gavage as a 20% suspension in corn oil vehicle. Dose levels were 631, 794, 1000 or 1260 mg/kg/bw. Clinical signs of toxicity were reduced appetite and activity – three to five days in

survivors – followed by increasing weakness, collapse and death. Most deaths occurred within two days. Gross autopsy findings on decedents included lung hyperemia, slight liver discoloration and acute gastrointestinal inflammation. Survivors were sacrificed after a two-week recovery period. All viscera examined appeared normal in these animals.

Reference: Monsanto Y-73-287, Younger Laboratories, 1974

5.1.2 ACUTE INHALATION TOXICITY

Type: LC_0 **[ ]**; LC_{100} **[ ]**; LC_{50} **[ ]**; LCL_0 **[ ]**; Other **[ ]**
Species/strain:
Exposure time:
Value:
Method:
GLP: Yes **[ ]** No **[ ]** ? **[ ]**
Test substance: . . . . . , purity: . . . . . .
Remarks:
Reference:

5.1.3 ACUTE DERMAL TOXICITY

Type: LD_0 **[ ]**; LD_{100} **[ ]**; LD_{50} **[X]**; LDL_0 **[ ]**; Other **[ ]**
Species/strain: New Zealand Albino Rabbits
Value: >7940 mg/kg b.w.
Method: Defined Lethal Dose
GLP: Yes **[ ]** No **[ ]** ? **[X]** **Klimisch 2**
Test substance: Santoflex IP Lot #NO12-002, purity: >95%
Remarks: The test article was applied to the shaved skin of groups of male and female rabbits for 24-hours as a 40% suspension in corn oil. Doses wer either 5010 or 7940 mg/kg/bw. All animals survived until sacrifice. Clinical signs of toxicity were limited to reduced appetite and activity for three to five days. Following a two-week recovery period, the animals were sacrificed. All viscera examined appeared normal in all animals.
Reference: Monsanto Y-73-287, Younger Laboratories, 1974

***5.4 REPEATED DOSE TOXICITY**

Species/strain: Sprague-Dawley Albino Rats
Sex: Female **[ ]**; Male **[ ]**; Male/Female **[X]**; No data **[ ]**
Route of Administration: Oral/Dietary
Exposure period: 30 Days
Frequency of treatment: Daily
Post exposure observation period:
Dose: 0, 500, 1000, 1750 or 2500 ppm
Control group: Yes **[X]**; No **[ ]**; No data **[ ]**;
Concurrent no treatment **[X]**; Concurrent vehicle **[ ]**; Historical **[]**
NOEL: 500 ppm
LOEL: 1000 ppm
Results: In a 30-day range-finding study that preceeded a 90-day study, the test substance was administered orally, via dietary admixture, to groups of male and female rats (5/sex/group). Control animals received the standard laboratory diet. Physical observations, body weight and food consumption measurements were

performed on all animals pretest and at selected intervals during the study. Hematology and chemistry determinations were performed on all animals at study termination. There were no mortalities during the course of the study. After four weeks of treatment, all animals were sacrificed, selected organs were weighed, and organ/body weight ratios were calculated. Complete postmortem examinations were conducted on all animals. Differences from control in body weight gain, hematological effects, elevations in total serum protein and increased liver and spleen weights were noted in animals dosed at 1000 ppm and above. There were no significant differences in findings between control groups animals and those dosed at 500 ppm that were attributed to the test article.

Method: Dunnett, C.W., A Multiple Comparison Procedure for Comparing Several Treatments with a Control, Jour. Am. Stat. Assoc. 50: 1096-1121, 1955

GLP: Yes **[X]** No **[ ]** ? **[ ]** **Klimisch 1**

Test substance: Santoflex IP Lot# 7J111, purity: 97.2%

Reference: Monsanto BD-88-74, Bio/dynamics Inc. 1988

Species/strain: Sprague-Dawley Albino Rats

Sex: Female **[ ]**; Male **[ ]**; Male/Female **[X]**; No data **[ ]**

Route of Administration: Oral/Dietary

Exposure period: 90 Days

Frequency of treatment: Daily

Post exposure observation period:

Dose: 0, 180, 360 or 720 ppm

Control group: Yes **[ ]**; No **[ ]**; No data **[ ]**;
Concurrent no treatment **[X]**; Concurrent vehicle **[ ]**; Historical **[]**

NOEL: 180 ppm for males, Not determined for females

LOEL: 360 ppm for males, 180 ppm for females

Results: The test substance was administered orally, via dietary admixture, to groups of male and female rats (10/sex/group). Control animals received the standard laboratory diet. Physical observations, body weight and food consumption measurements were performed on all animals pretest and at selected intervals during the study. Hematology and chemistry determinations were performed on all animals at Months 1.5 and 3. One high-dose and one mid-dose female were found dead on test day 93 following collection of terminal blood samples. The cause of death was attributed to the stress of bleeding and not to the administration of the test article. There were no other mortalities during the course of the study. After three months of treatment, all animals were sacrificed, selected organs were weighed, and organ/body and organ/brain weight ratios were calculated. Complete postmortem examinations were conducted on all animals. Histopathological evaluation of selected tissues was performed on all control and high-dose animals. The lungs, spleen, liver and kidneys were examined microscopically for all animals in all groups. Mean body weights and mean body weight gains were slightly reduced (2-4%) in males at 750 ppm.

Treatment-related findings were observed in several hematology parameters in the males and/or females at dose levels of 360 and 720 ppm. Parameters affected included reduced hemoglobin concentrations and hematocrit values at Week 6, reduced hemoglobin concentration in 720 ppm females at Week 13, elevated platelet counts in males at Week 6, and reduced mean erythrocyte counts in females at Week 6 and in high-dose females only at Week 13. The NOEL for hematology data was set at 180 ppm for both sexes. Differences in clinical chemistry parameters were noted in all mid- to high-dose animals. Mean liver weights, liver-to-body-weight and liver-to-brain-weight ratios were increased in 360 and 720 males, and in all treated females. There were no treatment-related findings noted in mortality, physical observations, opthalmology, food consumption or gross or microscopic pathology in any dose/sex group.

Method: OECD Guidelines for Testing of Chemicals, Section 453, 1981 and US EPA TSCA Section 4(a) Test Rules, 1982

GLP: Yes **[X]** No **[ ]** ? **[ ]** **Klimisch 1**

Test substance: Santoflex IP Lot# 7J111, purity: 97.2%

Reference: Monsanto BD-88-389, Bio/dynamics, Inc. 1990

*5.5 GENETIC TOXICITY IN VITRO

A. BACTERIAL TEST

Type: Bacterial Reverse Mutation - Ames

System of testing: TA-98, TA-100, TA-1535, TA-1537, TA-1538

Concentration: 0.1, 1,10, 100 and 500 micrograms/plate

Metabolic activation: With **[ ]**; Without **[ ]**; With and Without **[X]**; No data **[ ]**

Results:

Cytotoxicity conc: With metabolic activation: 500 ug/plate
Without metabolic activation: 500 ug/plate

Precipitation conc: Not determined

Genotoxic effects:

	+	?	-
With metabolic activation:	**[ ]**	**[ ]**	**[X]**
Without metabolic activation:	**[ ]**	**[ ]**	**[X]**

Method: Ames Plate Test (Overlay method) 1975; OECD 471 equivalent

GLP: Yes **[ ]** No **[ ]** ? **[X]** **Klimisch 2**

Test substance: Santoflex IP 11-02-76, purity: >95%

Remarks: Stock solutions prepared in DMSO. No evidence of mutagenic activity in any assay conducted with or without activation using the S-9 homogenate from Arochlor-induced rat livers.

Reference: Monsanto BIO-76-226, Litton Bionetics, 1976

Type: Bacterial Reverse Mutation - Ames

System of testing: TA-98, TA-100, TA-1535, TA-1537

Concentration: 0.2, 0.8, 4, 20, 60 and 200 micrograms/plate

Metabolic activation: With **[ ]**; Without **[ ]**; With and Without **[X]**; No data **[ ]**

Results:

Cytotoxicity conc: With metabolic activation: 200 ug/plate

Without metabolic activation: 200 ug/plate

Precipitation conc: Insoluble at 1 mg/plate and above

Genotoxic effects:

	+	?	-
With metabolic activation:	**[ ]**	**[ ]**	**[X]**
Without metabolic activation:	**[ ]**	**[ ]**	**[X]**

Method: Ames Plate Test (Overlay method) 1975; OECD 471 equivalent

GLP: Yes **[X]** No **[ ]** ? **[ ]** **Klimisch 1**

Test substance: Santoflex IP Lot# ND02-740, purity: 92-99%

Remarks: Stock solutions prepared in DMSO. No evidence of mutagenic activity in any assay conducted with or without activation using the S-9 homogenate from Arochlor-induced rat livers.

Reference: Monsanto ML-85-243, Environmental Health Labs, 1986

B. NON-BACTERIAL IN VITRO TEST

Type: Mammalian Cell Gene Forward Mutation Assay

System of testing: L5178Y Mouse Lymphoma cells

Concentration: 0.156, 0.313, 0.625, 1.250, 2.500 (without activation)
0.625, 1.250, 2.500, 5.000 and 10.000 (with activation)

Metabolic activation: With **[ ]**; Without **[ ]**; With and Without **[X]**; No data **[ ]**

Results:

Cytotoxicity conc: With metabolic activation: 10.0 ug/ml
Without metabolic activation: 2.5 ug/ml

Precipitation conc: >1 mg/ml

Genotoxic effects:

	+	?	-
With metabolic activation:	**[ ]**	**[ ]**	**[X]**
Without metabolic activation:	**[ ]**	**[ ]**	**[X]**

Method: Clive and Spector, Mutation Research 31:17-29 (1975)

GLP: Yes **[ ]** No **[ ]** ? **[X]** **Klimisch 2**

Test substance: Santoflex IP flakes Lot # N76-7433, purity 97%

Remarks: The test article was evaluated for specific locus forward mutation in the L5178Y Thymidine Kinase (TK) mouse lymphoma cell assay. Stock solutions were prepared in DMSO. DMSO was used as the negative control. EMS was used as the positive control without activation and DMN was used as the positive control with activation. The test article was found to be negative

Reference: Monsanto BIO-78-224 Litton Bionetics, 1978

Type: *In vitro* Unscheduled DNA Synthesis (UDS)

System of testing: Primary rat hepatocyte cultures (Fischer-344 strain)

Concentration: 0.01, 0.05, 0.1, 0.5, 1, 3, 5, 10, 50, 100, 1000 ug/ml

Metabolic activation: With **[ ]**; Without **[ ]**; With and Without **[X]**; No data **[ ]**

Results:

Cytotoxicity conc: Preliminary Assay: 5 ug/ml
Replicate Assay: 3 ug/ml

Precipitation conc: Separation/sticking to sides of tube noted at 100 ug/ml and above

Genotoxic effects:

+	?	-
[ ]	**[ ]**	**[X]**

Method: Williams, G.M., Detection of Chemical Carcinogens by Unscheduled DNA Synthesis in Rat Liver Primary Cell Cultures, Cancer Research 37, pp. 1845-1851 (1977)

GLP: Yes **[X]** No **[ ]** ? **[ ]** **Klimisch 1**

Test substance: Santoflex IP flakes Lot# ND02-740, purity 92-97%

Remarks: Acetone (1%) used as solvent and diluent. Primary rat liver cell cultures derived from the livers of two adult male rats. The positive control was 2-AAF, the solvent control was acetone in the preliminary assay and DMSO in the replicate assay. The percentage of cells in repair was calculated as the percentage of cells with at least 5 net grains/nucleus. 150 cells were scored for each concentration reported for each experiment. The net grain counts were negative at each concentration of the test compound, in the solvent control and in the medium control, in contrast to the strong positive response produced by the positive control 2-AAF in both experiments. These results indicate that Santoflex IP is not a genotoxic agent under the conditions of the in vitro rat hepatocyte DNA repair assay.

Reference: Monsanto SR-85-251, SRI International, 1986

Type: CHO/HGPRT Forward Gene Mutation Assay

System of testing: Cultured Chinese hamster ovary (CHO) cells

Concentration: 2, 5, 10, 15 and 30 ug/ml

Metabolic activation: With **[ ]**; Without **[ ]**; With and Without **[X]**; No data **[ ]**

Results:

Cytotoxicity conc: With metabolic activation: 30 ug/ml
Without metabolic activation: 10 ug/ml

Precipitation conc: Not Determined

Genotoxic effects:

	+	?	-
With metabolic activation:	**[ ]**	**[ ]**	**[X]**
Without metabolic activation:	**[ ]**	**[ ]**	**[X]**

Method: CHO/HGPRT Mutation Assay (1979) Hsie, et.al.

GLP: Yes **[X]** No **[ ]** ? **[ ]** **Klimisch 1**

Test substance: Santoflex IP Lot# N002-740, purity: 92-99%

Remarks: The mutagenic potential of Santoflex IP was tested in CHO cells for ability to induce forward mutation at the HGPRT gene locus. A range-finding cytotoxicity study preceded a dose-response mutagenicity experiment using different levels of Arochlor1254 rat liver homogenate (S9) concentrations, followed by a confirmatory dose-response mutagenicity experiment. The compound was tested at S9 concentrations up to a cytotoxic dose of 30 ug/ml. No statistically significant mutagenicity was observed in the two separate experiments. Therefore, the test substance was not considered to be mutagenic in CHO cells under the experimental conditions.

Reference: Monsanto ML-85-221, Environmental Health Labs, 1986

*** 5.6 GENETIC TOXICITY IN VIVO**

Type:

Species/strain:

Sex: Female **[ ]**; Male **[ ]**; Male/Female **[ ]**; No data **[ ]**

Route of Administration:

Exposure period:

Doses:

Results:

Effect on mitotic
index or P/N ratio:
Genotoxic effects: + ? -
[ ] [ ] [ ]

Method:
GLP: Yes **[ ]** No **[ ]** ? **[ ]**
Test substance: . . . . . , purity: . . . . . .
Remarks:
Reference:

***5.8 TOXICITY TO REPRODUCTION**

Type: Fertility **[]**; One-generation study **[]**; Two-generation study **[]**; Other **[ ]**
Species/strain:
Sex: Female **[ ]**; Male **[ ]**; Male/Female **[ ]**; No data **[ ]**
Route of Administration:
Exposure period:
Frequency of treatment:
Post exposure observation period:
Premating exposure period: male: . . . . . , female:
Duration of the test: .
Doses:
Control group: Yes **[ ]**; No **[ ]**; No data **[ ]**;
Concurrent no treatment **[ ]**; Concurrent vehicle **[ ]**; Historical **[ ]**
NOEL Parental:
NOEL F1 Offspring:
NOEL F2 Offspring:
Results: General parental toxicity
Toxicity to offspring:
Method:
GLP: Yes **[ ]** No **[ ]** ? **[ ]**
Test substance: . . . . . , purity: . . . . . .
Remarks:
Reference:

***5.9 DEVELOPMENTAL TOXICITY/ TERATOGENICITY**

Species/strain: Sprague-Dawley CD Rats
Sex: Female **[X]**; Male **[ ]**; Male/Female **[ ]**; No data **[ ]**
Route of Administration: Oral gavage
Duration of the test: 20 days from mating to C-section
Exposure period: Day 6-15 of gestation
Frequency of treatment: Daily, as a single oral dose at a volume of 5 ml/kg
Doses: 0, 12.5, 62.5 and 125 mg/kg/bw
Control group: Yes **[X]**; No **[ ]**; No data **[ ]**;
Concurrent no treatment **[]**; Concurrent vehicle **[X]**; Historical **[]**
NOEL Maternal Toxicity: 62.5 mg/kg
NOEL teratogenicity : 62.5 mg/kg
Results: The test substance was administered to groups of 24 pregnant rats during the period of embryo organogenesis. The vehicle was Polyethylene Glycol 400, and dose levels were 0, 12.5, 62.5 or 125 mg/kg/bw.

Maternal general toxicity: High-dose rats exhibited slight maternal toxicity as evidenced by a reduction in food intake, pre-dosing salivation and soft, dark feces. There were no effects on body weight. All animals survived to sacrifice. There were no treatment-related macroscopic findings at necropsy for any dose level.
Pregnancy/litter data: There were no treatment-related effects on uterine/implantation.
Foetal data: At 125 mg/kg there were statistically significant effects on the incidence of skeletal findings. Effects included an increased incidence of irregularly and incompletely ossified cranial and facial bones, and increased incidence of no ossification of hyoid, unilateral/bilateral wavy ribs, and semi-bipartite vertebral centra. At 62.5 mg/kg, there was a statistically significant increase in incomplete ossification of more than one cranial bone. At 12.5 mg/kg, there was a statistically significant increase in the incomplete ossification of more than one facial bone that was not considered to be treatment-related.

Method: OECD 59B (1982)
GLP: Yes **[X]** No **[ ]** ? **[ ]** **Klimisch 1**
Test substance: Santoflex IP dark flakes, Lot#2F054, purity: 97%
Remarks: No deviations from protocol noted.
Reference: Monsanto SP-93-46, SafePharm Laboratories 1994

5.10 OTHER RELEVANT INFORMATION

A. Specific toxicities

Type: Immunotoxicity
Repeat Insult Patch Test

Results: Santoflex IP, 50% w/v in Dimethylphthalate, was applied to the upper arm of 50 human volunteers using a linteen disk moistened with the test material. The patch was kept in place for 24 hours before removal and grading of gross skin changes on a scale of 0-4. After a 24-hour rest period, the test material was reapplied. This cycle was repeated every Monday, Wednesday and Friday, with a 48-hour rest period over weekends. After the 15th application, the volunteers rested two weeks before the challenge application.

Application #1:	Score 0/50
Applications #2-15:	Score 10/50
Challenge:	Score 11/50

Remarks: Under the test conditions, 11/50 or 22% of the volunteers showed sensitization responses. Those 11 persons were also subjected to a supplementary challenge using Santoflex 13 (6PPD). No subject showed any indication of cross-sensitization from one PPD rubber chemical material to another.
Reference: Monsanto SH-76-7, Product Investigations, Inc. 1976

Type: Immunotoxicity
Modified Draize Skin Sensitization Study on Human Volunteers
Results: The study was performed over a 6-week period on 82 human

volunteers using Santoflex IP, 1%, in petrolatum. During the first three weeks, patches moistened with the test material were applied to the arms at the same site at the rate of three times/week. Following a rest period, a challenge application was made to a different site. Results for irritation and sensitization were scored on a scale of 0-4. 12 of 82 test subjects were deemed to be sensitized, for a rate of 14.6%

Reference: Monsanto MA-78-92, 1978

B. Toxicodynamics, toxicokinetics

Type: .
Results:
Remarks:
References:

*** 5.11 EXPERIENCE WITH HUMAN EXPOSURE**

Results:
Remarks:
Reference:

6. REFERENCES

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8. Lyman, W.J. et. al., Handbook of Chemical Property Estimation Methods, Washington, D.C., American Chemical Society, pp 4-9 15-1 to 15-29, 1990
9. Monsanto ABC-32301, Santoflex IP Phase I Hydrolysis Study: Identification of Hydrolysis Products, Analytical Bio-Chemistry Laboratories, Inc., March 10, 1986
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11. Monsanto BN-76-255, Acute (96 hour) Toxicity of Santoflex IP to Rainbow Trout and Bluegill, EG&G Bionomics Aquatic Toxicity Laboratory, January 1977
12. Monsanto AB-78-120B, Dynamic Toxicity of Santoflex IP to Fathead Minnows, Analytical Bio-Chemistry Laboratories, Inc. July 30, 1979
13. Monsanto 9AB981013, Acute Toxicity of Santoflex IP to Midge, Analytical Bio-Chemistry laboratories, Inc. September 18, 1981
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19. Monsanto BD-88-389, A Subchronic (3 Month) Oral Toxicity Study with Santoflex IP in the Rat via Dietary Admixture, Bio/dynamics, Inc., June 1990
20. Monsanto BIO-76-226, Mutagenicity Evaluation of Santoflex IP, Litton Bionetics, Inc. December 30, 1976
21. Monsanto ML-85-243, Ames/Salmonella Mutagenicity Assay of Santoflex IP, Monsanto Environmental Health Laboratory, February 18, 1986
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25. Monsanto SP-93-46, IPPD: Oral Gavage Teratology Study in the Rat, SafePharm Laboratories, January 27, 1994
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I U C L I D

D a t a S e t

Existing Chemical	ID: 793-24-8
CAS No.	793-24-8
EINECS Name	N-1,3-dimethylbutyl-N'-phenyl-p-phenylenediamine
EINECS No.	212-344-0
TSCA Name	1,4-Benzenediamine, N-(1,3-dimethylbutyl)-N'-phenyl-
Molecular Formula	C18H24N2

Producer Related Part
Company:
Creation date: 23-SEP-1999

Substance Related Part
Company:
Creation date: 23-SEP-1999

Memo: RAPA PPD category

Printing date: 20-NOV-2001
Revision date:
Date of last Update: 20-NOV-2001

Number of Pages: 57

Chapter (profile): Chapter: 1, 2, 3, 4, 5, 7
Reliability (profile): Reliability: without reliability, 1, 2, 3, 4
Flags (profile): Flags: without flag, confidential, non confidential, WGK (DE), TA-Luft (DE), Material Safety Dataset, Risk Assessment, Directive 67/548/EEC, SIDS

1.0.1 OECD and Company Information

Type: lead organisation
Name: American Chemistry Council (formerly Chemical Manufacturers Association), Rubber and Plastic Additives Panel
Street: 1300 Wilson Boulevard
Town: 22209 Arlington, VA
Country: United States
Phone: 703-741-5600
Telefax: 703-741-6091

20-NOV-2001

Type: cooperating company
Name: Bayer Corporation
Country: United States

20-NOV-2001

Type: cooperating company
Name: Ciba Specialty Chemicals Corporation
Country: United States

20-NOV-2001

Type: cooperating company
Name: Crompton Corporation
Country: United States

20-NOV-2001

Type: cooperating company
Name: Flexsys America L.P.
Country: United States

20-NOV-2001

Type: cooperating company
Name: Noveon, Inc. (formerly BF Goodrich)
Country: United States

20-NOV-2001

Type: cooperating company
Name: R.T. Vanderbilt Company, Inc.
Country: United States

20-NOV-2001

Type: cooperating company
Name: The Goodyear Tire & Rubber Company
Country: United States

20-NOV-2001

Type: cooperating company
Name: The Lubrizol Corporation
Country: United States

20-NOV-2001

Type: cooperating company
Name: UOP, LLC.
Country: United States

20-NOV-2001

1.0.2 Location of Production Site
-

1.0.3 Identity of Recipients
-

1.1 General Substance Information
-

1.1.0 Details on Template
-

1.1.1 Spectra
-

1.2 Synonyms
-

1.3 Impurities
-

1.4 Additives
-

1.5 Quantity
-

1.6.1 Labelling
-

1.6.2 Classification
-

1.7 Use Pattern
-

1.7.1 Technology Production/Use
-

1.8 Occupational Exposure Limit Values
-

1.9 Source of Exposure
-

1.10.1 Recommendations/Precautionary Measures
-

1.10.2 Emergency Measures
-

1.11 Packaging
-

1.12 Possib. of Rendering Subst. Harmless
-

1.13 Statements Concerning Waste
-

1.14.1 Water Pollution
-

1.14.2 Major Accident Hazards
-

1.14.3 Air Pollution
-

1.15 Additional Remarks
-

1.16 Last Literature Search
-

1.17 Reviews
-

1.18 Listings e.g. Chemical Inventories
-

2.1 Melting Point

Value: 45 degree C
Decomposition: no
Sublimation: no
Method: other: FF83.9-1 Initial and Final Melting Point of Organic Compounds.
Year: 1996
GLP: yes
Testsubstance: other TS: CAS# 793-24-8
Remark: Capillary method
Reliability: (1) valid without restriction
GLP guideline study
Flag: Critical study for SIDS endpoint
20-NOV-2001 (1)

Value: 50 degree C
Method: other: Handbook value
GLP: no data
Testsubstance: other TS: CAS# 793-24-8
Reliability: (2) valid with restrictions
Data from Handbook or collection of data
Flag: Critical study for SIDS endpoint
20-NOV-2001 (2)

Value: 45 - 48 degree C
Source: Bayer AG Leverkusen
20-NOV-2001 (3)

2.2 Boiling Point

Value: 230 degree C at 13.3 hPa
Source: Bayer AG Leverkusen
28-SEP-1992 (3)

2.3 Density

Type: relative density
Value: 1 at 15 degree C
Method: other: FF97.8-1 Flexsys Standard Method
Year: 1997
GLP: yes
Testsubstance: other TS: CAS# 793-24-8
Remark: Density of solids by displacement
Flag: Critical study for SIDS endpoint
20-NOV-2001 (4)

Type:
Value: 1.02 g/cm3 at 20 degree C
Source: Bayer AG Leverkusen
28-SEP-1992 (3)

Type:
Value: .995 g/cm3 at 50 degree C
Source: Bayer AG Leverkusen
20-JUN-1997 (5)

Type: relative density
Value: 1 at 60 degree C
Source: MonsantoBayer AG Leverkusen
26-MAY-1994

2.3.1 Granulometry
-

2.4 Vapour Pressure

Value: 8.7 hPa at 200 degree C
Source: Bayer AG Leverkusen
28-SEP-1992 (3)

Value: 93 hPa at 300 degree C
Source: Bayer AG Leverkusen
28-SEP-1992 (3)

2.5 Partition Coefficient

log Pow: 4.68 at 25 degree C
Method: other (calculated): SRC LogKow (KowWin) Program
Year: 1995
GLP: no
Testsubstance: other TS: molecular structure
Reliability: (2) valid with restrictions
Accepted calculation method
Flag: Critical study for SIDS endpoint
20-NOV-2001 (6)

log Pow: 5.4
Method: other (calculated): Leo, A.: CLOGP-3.54 MedChem Software 1989. Daylight, Chemical Information Systems, Claremont, CA 91711, USA
Year:
Source: Bayer AG Leverkusen
Reliability: (2) valid with restrictions
20-NOV-2001 (7)

log Pow:
Method:
Year:
Remark: pow = 59000 +/- 34000
Source: Bayer AG Leverkusen
14-JAN-1993 (8)

2.6.1 Water Solubility

Value:	1.1 other: ppm at 23 degree C
Qualitative:	not soluble
Method:	other: Saturated Solution / Solvent Extraction / GC.Analysis
GLP:	no data
Testsubstance:	other TS: CAS# 793-24-8
Remark:	CH2Cl2 solvent, 96% recovery at 1 ppm. Equilibrated w/out light.
Reliability:	(2) valid with restrictions Meets generally accepted scientific standards, well documented and acceptable for assessment
Flag:	Critical study for SIDS endpoint

20-NOV-2001 (9) (10)

Value:	ca. 1 mg/l at 50 degree C
Method:	other: modified OECD Guideline 105 "Water solubility-Flask Method"
Source:	Bayer AG Leverkusen
Reliability:	(2) valid with restrictions Meets generally accepted scientific standards, well documented and acceptable for assessment

20-NOV-2001 (5)

2.6.2 Surface Tension

-

2.7 Flash Point

Value:	200 degree C
Type:	closed cup
Method:	other: DIN 51758
Year:	
Source:	Bayer AG Leverkusen

28-SEP-1992 (3)

2.8 Auto Flammability

-

2.9 Flammability

Result:	
Remark:	no information
Source:	Bayer AG Leverkusen

04-FEB-1992

2.10 Explosive Properties

-

2.11 Oxidizing Properties
-

2.12 Additional Remarks
-

3.1.1 Photodegradation

Type: air
INDIRECT PHOTOLYSIS
Sensitizer: OH
Conc. of sens.: 1560000 molecule/cm3
Rate constant: .0000000002264928 cm3/(molecule * sec)
Degradation: 50 % after .6 hour(s)
Method: other (calculated): AOP Program (v1.89)
Year: 1999 GLP: no
Test substance: other TS: molecular structure
Reliability: (2) valid with restrictions
Accepted calculation method
Flag: Critical study for SIDS endpoint
20-NOV-2001 (11)

Type: air
INDIRECT PHOTOLYSIS
Sensitizer: OH
Method: other (calculated): calculation according to Atkinson
Year: GLP:
Test substance: other TS: CAS# 793-24-8
Remark: t1/2 = 1.1 h
Source: Bayer AG Leverkusen
Reliability: (2) valid with restrictions
Accepted calculation method
Flag: Critical study for SIDS endpoint
20-NOV-2001

3.1.2 Stability in Water

Type: abiotic
Degradation: 93 % after 24 hour(s)
at pH 70 and 25 degree C
Deg. Product: yes
Method: other: Phase I Hydrolysis Study / ID of Hydrolysis Products
Year: GLP: yes
Test substance: other TS: Purple solid # KD08-281 purity: >95%
Remark: Rapid hydrolysis to 4-Hydroxylamine and
Benzoquinoneimine-N-phenyl.
Reliability: (1) valid without restriction
GLP study, meets generally accepted scientific standards, well documented and acceptable for assessment
Flag: Critical study for SIDS endpoint
20-NOV-2001 (12)

Type: abiotic
Degradation: = 60 % after 25 hour(s)
Method: other: Monsanto Laboratory protocol; see test conditions
Year: 1978 GLP: no data
Test substance:
Remark: Degradation data versus time: 0 hour 1 mg/l, 1 hour 0.855 mg/l, 2 hour 0.846 mg/l, 3.5 hour 0.636 mg/l and 25 hour 0.402 mg/l
Source: MonsantoBayer AG Leverkusen
Test condition: Degradation of test substance in deionized water
Reliability: (2) valid with restrictions
20-OCT-1999 (13)

Type: abiotic
t1/2 pH7: = 3 - 4 hour(s) at 24 degree C
Method: other: Monsanto Laboratory protocol; see test conditions
Year: 1993 GLP: yes
Test substance:
Remark: Santoflex 13 is an antiozonant and as such necessarily reacts very quickly with oxygen. Therefore, fast oxidation in dilute solutions, where oxygen is readily available, is to be expected. The initial oxidation product is believed to be quinondiimine, which itself is a very reactive species. The quinondiimine can hydrolyze or form a polymer by further oxidation giving very complicated mixtures of products usually involving loss of the alkyl group.
Source: MonsantoBayer AG Leverkusen
Test condition: Degradation in pH 7 buffered deionized water
30-MAY-1994 (14)

3.1.3 Stability in Soil

Type: Radiolabel:
Concentration:
Cation exch. capac.
Microbial biomass:
Method:
Year: GLP:
Test substance:
Remark: no information
Source: Bayer AG Leverkusen
12-JUN-1992

3.2 Monitoring Data (Environment)

Type of measurement:
Medium:
Method:
Concentration
Remark: no information
Source: Bayer AG Leverkusen
06-FEB-1992

3.3.1 Transport between Environmental Compartments

Type: fugacity model level III
Media: other: air, water, soil, sediment
Air (Level I):
Water (Level I):
Soil (Level I):
Biota (L.II/III):
Soil (L.II/III):
Method: other: EPIWIN Level III Fugacity Model
Year: 1999
Result:

Media	Concentration (percent)	Half-Life (hr)	Emissions (kg/hr)	Fugacity (atm)
Air	0.0264	1.13	1000	6.66e-013
Water	19.6	900	1000	3.36e-014
Soil	68.1	900	1000	2.84e-015
Sediment	12.2	3.6e+003	0	2.28e-014

Media	Reaction (kg/hr)	Advection (kg/hr)	Reaction (percent)	Advection (percent)
Air	457	7.47	15.2	0.249
Water	427	555	14.2	18.5
Soil	1.48e+003	0	49.4	0
Sediment	66.2	6.88	2.21	0.229

Persistence Time: 941 hr
Reaction Time: 1.16e+003 hr
Advection Time: 4.96e+003 hr
Percent Reacted: 81
Percent Advected: 19

Reliability: (2) valid with restrictions
Accepted calculation method
Flag: Critical study for SIDS endpoint
20-NOV-2001 (11)

3.3.2 Distribution

Media: air - biota - sediment(s) - soil - water
Method: other (calculation): Fugacity Level III
Year: 1999
Result:

	Concentration (percent)	Half-Life (hr)	Emissions (kg/hr)
Air	0.0264	1.13	1000
Water	19.6	900	1000
Soil	68.1	900	1000
Sediment	12.2	3600	0

Pers
Reliability: (2) valid with restrictions
21-OCT-1999 (15)

Media:
Method:
Year:
Remark: Based on the calculated log Pow, transport of the compound from water to soil/sediment (geoaccumulation) is to be expected.
Water solubility and vapour pressure indicate that the transport from water to air is of low relevance.
Source: Bayer AG Leverkusen
21-OCT-1999

3.4 Mode of Degradation in Actual Use

Remark: no information
Source: Bayer AG Leverkusen
06-FEB-1992

3.5 Biodegradation

Type: aerobic
Inoculum: other: Mississippi River water
Concentration: 1.002 mg/l related to Test substance
Degradation: = 97 % after 22 hour(s)
Result: other: Primary degradation, 96 % primary degradation in sterile river water and 88 % in deionized water in 22 hours
Testsubstance: 1 hour(s) = 40 %
2 hour(s) = 57 %
3 hour(s) = 67 %
4 hour(s) = 62 %
5 hour(s) = 74 %
Method: other: Natural Water Die-Away in Mississippi River water
Year: GLP: yes
Test substance: other TS: Santoflex 13 Lot# KD-03017, purity: >95%
Remark: Rate of disappearance in

time	active Mississippi River water	sterile Mississippi River water	deionized water
0 hour	100 %	100 %	100 %
1 hour	60 %	85 %	100 %
2 hour	43 %	70 %	88 %
3 hour	33 %	56 %	86 %
4 hour	38 %	49 %	80 %
5 hour	26 %	41 %	65 %
22 hour	3 %	4 %	12 %

Result: 50% degradation after 2.9 hours
Reliability: (1) valid without restriction
GLP study, meets generally accepted scientific standards, well documented and acceptable for assessment
Flag: Critical study for SIDS endpoint
20-NOV-2001 (16)

Type: aerobic
Inoculum: predominantly domestic sewage
Degradation: 13 - 40 % after 28 day
Method: other: Respirometer-Test, ISO DP 9408, EG Directive 79/831/ Annex V, modified MITI Test
Year: GLP: no
Test substance: other TS
Source: Bayer AG Leverkusen
Test substance: technical grade 6PPD
20-NOV-2001 (17)

Type: aerobic
Inoculum: activated sludge
Concentration: 30 mg/l related to Test substance
Degradation: = 7.2 % after 32 day
Result: other: 7.2 % CO2 evolution in 32 days
Method: other: Method similar to Gledhill method listed in U.S.E.P.A. 40 CFR Ch 1 subpart D paragraph 796.3100.
Year: GLP: no data
Test substance:
Source: MonsantoBayer AG Leverkusen
20-NOV-2001 (13)

3.6 BOD5, COD or BOD5/COD Ratio
-

3.7 Bioaccumulation
-

3.8 Additional Remarks

Remark: 1.4-Benzenediamine, N-(1.3-dimethylbutyl)-N'-phenyl decreases the degradation rate of unprotected rubber (vulcanisate) in water.
Source: Bayer AG Leverkusen
01-DEC-1992 (18)

AQUATIC ORGANISMS

4.1 Acute/Prolonged Toxicity to Fish

Type: static
Species: Salmo gairdneri (Fish, estuary, fresh water)
Exposure period: 96 hour(s)
Unit: mg/l Analytical monitoring: yes
LC50: = .14
Method: other: EPA Methods for Acute Toxicity Tests with Fish, Macroinvertebrates and Amphibians.
Year: 1977 GLP: no data
Test substance: other TS: Santoflex 13 Lot# KD03-017, purity: >95%.
Remark: Solutions in reagent-grade acetone; Water quality parameters monitored throughout test.
Result: 96 hr C.I. = 0.12 - 0.16 mg/l;
24 hr LC50 = 0.28 mg/l;
48 hr LC50 = 0.18 mg/l
Test condition: carrier-acetone; 15L water; 10 fish/vessel; length = 3.7 cm; no food; no aeration; temp = 12C
Reliability: (1) valid without restriction
Guideline study
Flag: Critical study for SIDS endpoint
20-NOV-2001 (19)

Type: static
Species: Lepomis macrochirus (Fish, fresh water)
Exposure period: 96 hour(s)
Unit: mg/l Analytical monitoring: yes
LC50: .4
Method: other: EPA Methods for Acute Toxicity Tests with Fish, Macroinvertebrates and Amphibians.
Year: 1977 GLP: no data
Test substance: other TS: Santoflex 13 Lot# KD03-017, purity: >95%.
Remark: Solutions in reagent-grade acetone; Water quality parameters monitored throughout test.
Result: 96 hr C.I. = 0.32 - 0.5 mg/l;
24 hr LC50 = 0.65 mg/l;
48 hr LC50 = 0.45 mg/l
Test condition: carrier-acetone; 15L water; 10 fish/vessel; length = 3.8 cm; no food; no aeration; temp = 22C
Reliability: (1) valid without restriction
Guideline study
Flag: Critical study for SIDS endpoint
20-NOV-2001 (19)

Type: static
Species: Brachydanio rerio (Fish, fresh water)
Exposure period: 96 hour(s)
Unit: mg/l Analytical monitoring: no
LC0: 5
LC100: 100
Method: other: see remarks
Year: 1984 GLP: no
Test substance: other TS: technical grade 6PPD
Remark: following OECD 203
The powdered test substance was dispersed in water. LC-values given above are nominal concentrations: weight of the dispersed substance per liter water.
Source: Bayer AG Leverkusen
Reliability: (2) valid with restrictions
Meets generally accepted scientific standards, well documented and acceptable for assessment
20-NOV-2001 (20)

Type: flow through
Species: Pimephales promelas (Fish, fresh water)
Exposure period: 28 day
Unit: mg/l Analytical monitoring: yes
LC50: = .15
Method: other: EPA Methods for Acute Toxicity Tests with Fish, Macroinvertebrates and Amphibians.
Year: 1984 GLP: yes
Test substance: other TS: Santoflex 13 purity: >95%.
Remark: C.I. = 0.13 - 0.17 mg/l; 48 hr LC50 = 2 mg/l; 6, 7 and 8 day LC50 = 0.35 mg/l; 19, 20, 21 day LC50 = 0.17 mg/l
Tests in well water; Stock solutions in acetone; Water quality parameters monitored throughout test.
Result: 28D C.I. = 0.13 - 0.17 mg/l;
48 hr LC50 = 2 mg/l;
6, 7 and 8 day LC50 = 0.35 mg/l;
19, 20, 21 day LC50 = 0.17 mg/l
Reliability: (1) valid without restriction
GLP guideline study
20-NOV-2001 (21)

4.2 Acute Toxicity to Aquatic Invertebrates

Type:	static
Species:	Daphnia magna (Crustacea)
Exposure period:	48 hour(s)
Unit:	mg/l Analytical monitoring: yes
NOEC:	= .56
EC50:	= .82
Method:	other: EPA Methods for Acute Toxicity Tests with Fish, Macroinvertebrates and Amphibians
Year:	GLP: yes
Test substance:	other TS: Santoflex 13, purity: >95%
Remark:	Solutions in reagent-grade acetone; Water quality parameters monitored throughout test.
Result:	C.I. for 48 hr EC50=0.71-0.94 mg/l; 24 hr EC50=1 mg/l
Reliability:	(1) valid without restriction GLP study, meets generally accepted scientific standards, well documented and acceptable for assessment
Flag:	Critical study for SIDS endpoint

20-NOV-2001 (22)

Type:	
Species:	Daphnia magna (Crustacea)
Exposure period:	48 hour(s)
Unit:	mg/l Analytical monitoring: no
NOEC:	= .4
EC50:	= .79
Method:	OECD Guide-line 202, part 1 "Daphnia sp., Acute Immobilisation Test"
Year:	1984 GLP: no data
Test substance:	
Remark:	C.I. for EC50 = 0.7 - 0.91 mg/l; 24 hr EC50=1.6 mg/l; 48 hr EC50=0.79 mg/l; in presence of food 48 hr EC50= 1.3 mg/l and NOEC=0.4 mg/l
Source:	MonsantoBayer AG Leverkusen
Test condition:	carrier-acetone; no food
Reliability:	(1) valid without restriction Guideline study
Flag:	Critical study for SIDS endpoint

20-NOV-2001 (23)

Type:
Species: Daphnia magna (Crustacea)
Exposure period: 48 hour(s)
Unit: mg/l Analytical monitoring: no
NOEC: = .25
EC50: = .51
Method: OECD Guide-line 202, part 1 "Daphnia sp., Acute Immobilisation Test"
Year: 1984 GLP: no data
Test substance:
Remark: the test solution was allowed to age 40 hours before test 48 hr EC50>1 mg/l and NOEC>1 mg/l
Source: MonsantoBayer AG Leverkusen
Reliability: (1) valid without restriction
Guideline study
Flag: Critical study for SIDS endpoint
20-NOV-2001 (24)

Type:
Species: other: Chironomus tentans
Exposure period: 48 hour(s)
Unit: mg/l Analytical monitoring: no
NOEC: = .6
EC50: = .99
Method: other: EPA. Methods for Acute Toxicity Tests with Fish, Macroinvertebrates, and Amphibians. EPA-660/3-75-009.
Year: 1975 GLP: no data
Test substance:
Remark: C.I. for EC50=0.6-1.25 mg/l; 24hr EC50=1.25 mg/l
Source: MonsantoBayer AG Leverkusen
Test condition: water solubility was exceeded at three highest concentrations; larvae 10-14 days old; room temp
30-MAY-1994 (25)

4.3 Toxicity to Aquatic Plants e.g. Algae

Species: Selenastrum capricornutum (Algae)
Endpoint: biomass
Exposure period: 96 hour(s)
Unit: mg/l Analytical monitoring: yes
EC50: = .6
Method: other: EPA Selenastrum capricornutum Algal Assay Test
Year: 1971 GLP: no data
Test substance: other TS: Santoflex 13 (Monsanto) purity: >95%
Remark: Phytotoxicity maxed at 48 hours; test solutions in acetone
Result: 96 hr C.I. 0.2-2 mg/l;
in vivo chlorophyll results-
24hr EC50=2.0 mg/l,
48hr EC50=0.5 mg/l,
72hr EC50=0.5 mg/l,
96hr EC50=0.6 mg/l
Test condition: temp=24C; 4000 lux; Algal Assay media; "cool" white lights;
init. inoc.=10000 cells/ml
Reliability: (1) valid without restriction
Guideline study
Flag: Critical study for SIDS endpoint
20-NOV-2001 (26) (27)

4.4 Toxicity to Microorganisms e.g. Bacteria

Type:
Species: activated sludge
Exposure period: 3 hour(s)
Unit: mg/l Analytical monitoring:
EC50: 420
Method: ISO 8192 "Test for inhibition of oxygen consumption by
activated sludge"
Year: GLP: no
Test substance: other TS
Source: Bayer AG Leverkusen
Test substance: technical grade 6PPD
01-DEC-1992 (20)

4.5 Chronic Toxicity to Aquatic Organisms

4.5.1 Chronic Toxicity to Fish

Species:
Endpoint:
Exposure period:
Unit: Analytical monitoring:
Method:
Year: GLP:
Test substance:
Remark: no information
Source: Bayer AG Leverkusen
06-FEB-1992

4.5.2 Chronic Toxicity to Aquatic Invertebrates

Species:
Endpoint:
Exposure period:
Unit: Analytical monitoring:
Method:
Year: GLP:
Test substance:
Remark: no information
Source: Bayer AG Leverkusen
06-FEB-1992

TERRESTRIAL ORGANISMS

4.6.1 Toxicity to Soil Dwelling Organisms

Type:
Species:
Endpoint:
Exposure period:
Unit:
Method:
Year: GLP:
Test substance:
Remark: no information
Source: Bayer AG Leverkusen
06-FEB-1992

4.6.2 Toxicity to Terrestrial Plants

Species:
Endpoint:
Expos. period:
Unit:
Method:
Year: GLP:
Test substance:
Remark: no information
Source: Bayer AG Leverkusen
06-FEB-1992

4.6.3 Toxicity to other Non-Mamm. Terrestrial Species
-

4.7 Biological Effects Monitoring

Remark: no information
Source: Bayer AG Leverkusen
06-FEB-1992

4.8 Biotransformation and Kinetics

Type:
Remark: no information
Source: Bayer AG Leverkusen
06-FEB-1992

4.9 Additional Remarks
-

5.1 Acute Toxicity

5.1.1 Acute Oral Toxicity

Type:	LD50
Species:	rat
Strain:	Sprague-Dawley
Sex:	male/female
Number of Animals:	10
Vehicle:	
Value:	> 5000 mg/kg bw
Method:	other:EPA/TSCA Acute Oral Toxicity and the EEC Methods for Determining Toxicity, Part B.1, No. L 251/96 Sept. 1984
Year:	GLP: yes
Test substance:	other TS: 6PPD Ref# 4065459 solid, purity: 97.6%
Remark:	Following a range-finding study, 6PPD was fed to a group of five male and five female rats in a single oral dose of 5000 mg/kg body weight. Rats were observed daily and weighed weekly. 2 males and I female died prior to sacrifice. A gross necropsy examination was performed on all surviving animals at sacrifice on Day 15. Clinical findings included decreased fecal output, fecal/urine stains, rough coat, piloerection and soft stools. One male and three females showed weight loss; all other animals gained weight. Most notable internal necropsy finding was black, hard material in the stomach contents. Findings in animals that died included discolored mucoid contents throughout the digestive system with reddened mucosa/dark red foci of the stomach.
Reliability:	(1) valid without restriction GLP guideline study
Flag:	Critical study for SIDS endpoint

20-NOV-2001 (28)

Type:	LD50
Species:	rat
Strain:	
Sex:	
Number of Animals:	
Vehicle:	
Value:	= 3340 mg/kg bw
Method:	
Year:	GLP:
Test substance:	other TS: undiluted
Source:	Bayer AG Leverkusen

08-DEC-1992 (29)

Type: LD50
Species: rat
Strain:
Sex:
Number of
Animals:
Vehicle:
Value: = 2500 mg/kg bw
Method:
Year: GLP:
Test substance:
Source: Bayer AG Leverkusen
08-DEC-1992 (30)

Type: LD50
Species: rat
Strain:
Sex:
Number of
Animals:
Vehicle:
Value: = 3580 mg/kg bw
Method:
Year: GLP:
Test substance: other TS: purity 95.7 %
Source: Bayer AG Leverkusen
08-DEC-1992 (31)

Type: LD50
Species: mouse
Strain:
Sex:
Number of
Animals:
Vehicle:
Value: = 3200 mg/kg bw
Method:
Year: GLP:
Test substance:
Source: Bayer AG Leverkusen
08-DEC-1992 (30)

Type: LD50
Species:
Strain:
Sex:
Number of
Animals:
Vehicle:
Value: = 1120 mg/kg bw
Method:
Year: GLP:
Test substance:
Source: Bayer AG Leverkusen
08-DEC-1992 (32)

5.1.2 Acute Inhalation Toxicity
-

5.1.3 Acute Dermal Toxicity

Type: LD50
Species: rabbit
Strain: New Zealand white
Sex: male/female
Number of
Animals:
Vehicle: other: undiluted
Value: > 7940 mg/kg bw
Method: other: Defined Lethal Dose
Year: GLP: no data
Test substance: other TS: CP 22423 Lot# KC07-298, purity: >95%.
Remark: The undiluted test article was applied to the shaved skin of male and female rabbits at dose levels ranging from 3160 to 7940 mg/kg/bw. Clinical signs were reduced appetite and activity for three to seven days. All animals survived. Autopsy results showed that all viscera appeared normal.
Reliability: (2) valid with restrictions
Meets generally accepted scientific standards, well documented and acceptable for assessment
Flag: Critical study for SIDS endpoint
20-NOV-2001 (31)

Type: LDLo
Species: rabbit
Strain:
Sex:
Number of
Animals:
Vehicle:
Value: 3160 - 5010 mg/kg bw
Method:
Year: GLP:
Test substance: other TS: undiluted
Source: Bayer AG Leverkusen

08-DEC-1992 (29)

5.1.4 Acute Toxicity, other Routes
-

5.2 Corrosiveness and Irritation

5.2.1 Skin Irritation

Species: rabbit
Concentration:

Exposure:
Exposure Time:
Number of
Animals:
PDII:
Result: slightly irritating
EC classificat.:
Method: Draize Test
Year: GLP:
Test substance: other TS: undiluted
Remark: method: the data were scored according to the method of Draize et al. (1944), 24 h exposure, then skin rinsed with warm water and soap, observation period 5 days
Source: Bayer AG Leverkusen
08-DEC-1992 (29)

Species: rabbit
Concentration:

Exposure:
Exposure Time:
Number of
Animals:
PDII:
Result: slightly irritating
EC classificat.:
Method: Draize Test
Year: GLP:
Test substance: other TS: 12.5 and 125 mg 6PPD dispersed in 0.5 g vaseline (2.5 and 25 %)
Remark: method: after 24 h and 72 h examination
Source: Bayer AG Leverkusen
08-DEC-1992 (33)

Species: rabbit
Concentration:

Exposure:
Exposure Time:
Number of
Animals:
PDII:
Result: moderately irritating
EC classificat.:
Method: Draize Test
Year: GLP:
Test substance: other TS: 25 mg 6PPD dispersed in 0.5 ml olive oil
Remark: method: after 24 h and 72 h examination
Source: Bayer AG Leverkusen
08-DEC-1992 (33)

Species: rabbit
Concentration:

Exposure:
Exposure Time:
Number of
Animals:
PDII:
Result: not irritating
EC classificat.:
Method: other: (see remarks)
Year: GLP:
Test substance:
Remark: method: 0.5 ml, semi-occlusive, clipped intact and abraded skin, 24 h exposure, observation period 7 days, scoring in accordance with the Federal Hazardous Substance Act, 21 CFR, paragraph 191.11 (1964)
Source: Bayer AG Leverkusen
08-DEC-1992 (31)

5.2.2 Eye Irritation

Species: rabbit
Concentration:
Dose:
Exposure Time:
Comment:
Number of
Animals:
Result: slightly irritating
EC classificat.:
Method: other: (see remarks)
Year: GLP:
Test substance: other TS: undiluted
Remark: method: 0.1 ml in the conjunctival sac of the right eye of each of 3 rabbits, 24 h exposure, then eyes rinsed with warm isotonic saline solution, observation period 5 days, the

data were scored according to the method of Draize et al. (1944)
Source: Bayer AG Leverkusen
08-DEC-1992 (29)

Species: rabbit
Concentration:
Dose:
Exposure Time:
Comment:
Number of Animals:
Result: slightly irritating
EC classificat.:
Method: other: (see remarks)
Year: GLP:
Test substance:
Remark: method: 0.1 ml in the conjunctival sac, observation period 7 days, scoring in accordance with the Federal Hazardous Substance Act, 21 CFR, paragraph 191.12 (1964)
Source: Bayer AG Leverkusen
08-DEC-1992 (31)

5.3 Sensitization

Type: Guinea pig maximization test
Species: guinea pig
Number of Animals:
Vehicle:
Result: sensitizing
Classification:
Method:
Year: GLP:
Test substance: other TS: 6PPD in olive oil or vaseline
Remark: 50 % sensitization (challenge with 0.05 %), 90 % sensitization (challenge with 0.5 %)
Source: Bayer AG Leverkusen
08-DEC-1992 (33)

Type: Patch-Test
Species: human
Concentration: Induction 50 %
Number of Animals: 50
Vehicle:
Result:
Classification:
Method: other: Modified Draize
Year: GLP:
Test substance: other TS: PPD; purity not stated
Remark: PPD was patch tested on 50 human volunteers at a concentration of 50% w/v in dimethylphthalate. 5 of the 50 subjects showed skin reactions during the 3-week induction phase of the study.

5 of 50 subjects showed skin reactions in the challenge phase.
20-NOV-2001 (34)

Type: Patch-Test
Species: human
Number of Animals:
Vehicle:
Result:
Classification:
Method: other: Repeated Insult Patch Test
Year: GLP:
Test substance: other TS: a 0.1 % W/V solution in dimethylphthalate
Remark: 0/50 volunteers had a positive test result
Source: Bayer AG Leverkusen
08-DEC-1992 (35)

Type: Patch-Test
Species: human
Number of Animals:
Vehicle:
Result:
Classification:
Method:
Year: GLP:
Test substance: other TS
Remark: 0/50 (for each rubber sample) human subjects not previously exposed to test rubber formulations had a positive patch test result
Source: Bayer AG Leverkusen
Test substance: 2 parts 6-PPD per hundred parts rubber, unvulcanized
2 parts 6-PPD per hundred parts rubber, vulcanized
20-MAY-1992 (36)

Type: Patch-Test
Species: human
Number of Animals:
Vehicle:
Result:
Classification:
Method:
Year: GLP:
Test substance: other TS: a rubber sample with 6PPD as additive
Remark: 17/50 subjects showed a positive reaction after challenge
Source: Bayer AG Leverkusen
08-DEC-1992 (37)

Type: Patch-Test
Species: human
Number of Animals:
Vehicle:
Result:
Classification:
Method:
Year: GLP:
Test substance: other TS: a rubber sample with 2 parts 6PPD per hundred parts rubber
Remark: 2/4 volunteer subjects who had reacted to previous rubber samples, had a positive patch test result
Source: Bayer AG Leverkusen
08-DEC-1992 (38)

Type: Patch-Test
Species: human
Number of Animals:
Vehicle:
Result:
Classification:
Method:
Year: GLP:
Test substance: other TS: a rubber sample with 2 parts 6PPD per hundred parts rubber
Remark: 5/10 volunteer subjects who had reacted to previous rubber samples, had a positive patch test result
Source: Bayer AG Leverkusen
08-DEC-1992 (39)

Type: Patch-Test
Species: human
Number of Animals:
Vehicle:
Result:
Classification:
Method:
Year: GLP:
Test substance: other TS: a rubber sample with 6PPD as additive
Remark: 3/10 volunteer subjects, all of whom had been previously sensitized to a rubber sample, had a positive patch test result
Source: Bayer AG Leverkusen
08-DEC-1992 (40)

Type: Patch-Test
Species: human
Number of Animals:
Vehicle:
Result:
Classification:
Method:
Year: GLP:
Test substance: other TS: samples with 1, 2 and 3 parts 6PPD per hundred parts rubber
Remark: 9/10 (for each rubber sample) volunteer subject who had reacted to previous rubber samples, had a positive patch test result
Source: Bayer AG Leverkusen
08-DEC-1992 (41)

Type: Patch-Test
Species: human
Number of Animals:
Vehicle:
Result:
Classification:
Method:
Year: GLP:
Test substance: other TS: a rubber sample with 6PPD as additive
Remark: 4/50 subjects showed a positive reaction after challenge
Source: Bayer AG Leverkusen
08-DEC-1992 (42)

Type: Patch-Test
Species: human
Number of Animals:
Vehicle:
Result:
Classification:
Method:
Year: GLP:
Test substance: other TS: a rubber sample with 2 parts 6PPD per hundred parts rubber
Remark: 0/50 volunteer subjects, not previously associated with either chemical had a positive patch test result
Source: Bayer AG Leverkusen
08-DEC-1992 (43)

Type: Patch-Test
Species: human
Number of Animals:
Vehicle:
Result:
Classification:
Method:
Year: GLP:
Test substance: other TS: 1 % Santoflex 13 in petrolatum
Remark: No skin reactions were noted in a 6-week study on 94 human volunteers. The induction phase consisted of the application of 1% 6PPD in petrolatum to the same site, 3x/week for three weeks. In the challenge phase, the test article was applied at a previously unpatched site.
20-NOV-2001 (44)

Type: Patch-Test
Species: human
Number of Animals:
Vehicle:
Result:
Classification:
Method:
Year: GLP:
Test substance: other TS: 50 % w/v Santoflex 13 in dimethylphthalate
Remark: 50 human volunteers were patch tested with 50 % w/v Santoflex 13 in dimethylphthalate; five of the 50 individuals showed reactions in the 3-week induction phase and 5 of 50 showed reactions in the challenge phase
Source: MonsantoBayer AG Leverkusen
31-MAY-1994 (45)

Type: Patch-Test
Species: human
Number of Animals:
Vehicle:
Result:
Classification:
Method:
Year: GLP:
Test substance: no data
Remark: 6/9 contact dermatitis patients showed a positive reaction with 6PPD
Source: Bayer AG Leverkusen
17-AUG-1998 (46)

Type: Patch-Test
Species: human
Number of Animals:
Vehicle:
Result:
Classification:
Method:
Year: GLP:
Test substance: no data
Remark: 6/135 contact dermatitis patients showed a positive reaction with 6PPD
Source: Bayer AG Leverkusen
17-AUG-1998 (47)

Type: no data
Species: human
Number of Animals:
Vehicle:
Result:
Classification:
Method:
Year: GLP:
Test substance: other TS: 2 % in lanolin
Remark: 15/15 IPPD-allergic patients were positive in the test with 6-PPD
Source: Bayer AG Leverkusen
08-DEC-1992 (33)

Type: other: (see remarks)
Species: guinea pig
Number of Animals:
Vehicle:
Result: not sensitizing
Classification:
Method: other: (see remarks)
Year: GLP:
Test substance:
Remark: method: application daily for 20 days (50 % paste), back, for the challenge different concentrations 10, 20, 30, 50 and 100 %) were applied to new areas of the back (no further data available)
Source: Bayer AG Leverkusen
08-DEC-1992 (30)

5.4 Repeated Dose Toxicity

Species:	rat Sex: male/female
Strain:	Sprague-Dawley
Route of admin.:	oral feed
Exposure period:	13 w
Frequency of treatment:	daily
Post. obs. period:	no data
Doses:	250, 1000 or 2500 ppm (19, 75 or 188 mg/kg b.w./d)
Control Group:	yes, concurrent no treatment
NOAEL:	250 ppm
Method:	other: EHL Protocol 85087 Ref: Multiple Comparison Procedure for Comparing Several Treatments with a Control (1955)
Year:	GLP: yes
Test substance:	other TS: Santoflex 13 Lot#KE06-121, purity: 97.1%
Result:	Santoflex 13 was administered in feed to groups of 6 week old male and female rats at the above levels. Analyses via GC verified feeding levels of 0, 230, 950 and 2300 ppm. All animals survived the length of the study. Signs of toxicity during the study were limited to reduced feed consumption/body weight gain in the high-dose males and females and mid-level males. Anemia, lymphocytopenia and thrombocytosis were present in males and females, primarily at the two highest dose levels. Increases in total bilirubin in males, and total protein, albumin, globulin, calcium and/or cholesterol in both sexes were noted in high and some mid-dose level animals. Increased liver weights were observed at the two highest dose levels. There were no gross or microscopic lesions attributed to consumption of the test material. Females at low dose levels exhibited mild anemia at the interim sampling period, but all recovered by the end of the study. Therefore, the NOEL was considered to be 250 ppm.
Reliability:	(1) valid without restriction GLP guideline study
Flag:	Critical study for SIDS endpoint

20-NOV-2001 (48) (49)

Species:	rat Sex: male/female
Strain:	Sprague-Dawley
Route of admin.:	inhalation
Exposure period:	4 w (20 exposures)
Frequency of treatment:	6 h/d
Post. obs. period:	no data
Doses:	0.054, 0.236 or 0.477 mg/l
Control Group:	yes, concurrent no treatment
Method:	other: Subacute Dust Inhalation Study IBT #8562-09721 (Audited)
Year:	GLP: yes
Test substance:	other TS: Santoflex 13 Powder Lot #KD03-017, purity: 97.1%
Result:	4 groups of 5 male and 5 female young adult albino rats were exposed to either zero, low, intermediate or high dust concentrations of the test article. Test dusts were suspended in streams of clean, dry air, and introduced through the top center of exposure chambers and exhausted out the bottom. GC analytical testing confirmed concentrations and total weight of test dusts. All but one animal survived until sacrifice on Day 28. Hypoactivity was noted in all test groups. Mid and high-dose animals exhibited swollen snouts and scratching. Mean body weights of treated animals compared favorably with those of controls. Results of gross necropsy indicated increased liver and kidney weights of treated animals over those of controls. Lung weights were reduced in high-dose makes and mid-dose females. Mid-dose treated males exhibited increased spleen weights. No significant differences were noted in the weights of the brains, gonads and hearts of treated animals when compared to controls. No gross or histopathologic alterations attributed to the test article were observed in any of the treated animals. Mean corpuscular hemoglobin was reduced in high-dose males; elevations in SGPT and lowered glucose levels in mid- and high-dose males were correlated with increased relative liver weights; no treatment related gross lesions were noted at necropsy.
Reliability:	(1) valid without restriction GLP study, meets generally accepted scientific standards, well documented and acceptable for assessment
Flag:	Critical study for SIDS endpoint

20-NOV-2001 (50)

Species:	rat Sex: male/female
Strain:	other: Charles River CD
Route of admin.:	oral feed
Exposure period:	24 months
Frequency of treatment:	daily
Post. obs. period:	no
Doses:	100, 300, 1000 ppm (8, 23, 75 mg/kg b.w./day)
Control Group:	yes, concurrent no treatment
NOAEL:	23 mg/kg
LOAEL:	75 mg/kg
Method:	other: 2-Year Chronic Oral Toxicity IBT Protocol # 622-05400A (1974)
Year:	GLP: yes
Test substance:	other TS: 6PPD. Powder, purity: 96.9%
Remark:	hematology, clinical chemistry and urinalysis were conducted at 3, 6, 12 and 24 months, the calculation of the dose levels is based on 1 ppm corresponds to 0.075 mg/kg b.w.; 50 male and 50 female rats per group.
Result:	6PPD was fed at the above doses to groups of 200 male and 200 female rats over a two-year period, beginning when the males were 28 days old and the females 29 days old. Dose levels were verified by GC analysis. Body weight, food consumption, behavior, hematology, blood chemistry and urinalysis results were recorded throughout the study. Complete gross necropsies were conducted on all animals found dead, on all animals sacrificed in extremis, and on all remaining animals at 24 months. All organs or tissues with grossly visible lesions were submitted for histologic examination. Statistical reductions in body weight were noted in high-dose males during Weeks 1-5. High-dose females exhibited statistically reduced body weights throughout the study. Body weights and weight gain of the mid- to low-dose animals compared favorably to controls. Frequency and distribution of deaths during the study were similar between treated animals and controls. Gross pathological examination of animals that died during the study did not reveal any relation to death and the test article. There were no unusual behaviors noted in test animals during the study. A significant reduction in erythrocyte counts was noted in high-dose males at 3 months and in high-dose females at 3, 6, and 9 months. However, the same animals had erythrocyte counts similar to controls at all subsequent blood collections. Hemoglobin concentration, while still considered to be within normal range, was statistically reduced for high-dose males at 3, 12 and 18 months. High-dose females exhibited similar reductions at 6, 12 and 18 months. Hematocrit values among high-dose animals were significantly lower than controls, and were at the lower limits at 3 and 12 months for males, and 3,6 and 12 months for females. Hematocrit values in these animals exhibited a slight increase at 18 and 24 months. Urinalysis studies, which included monitoring of glucose, albumin, microscopic elements, pH and specific gravity, were similar for both treated and control

groups throughout the study. Gross pathological examination of animals sacrificed at 24 months revealed similar findings for both treated and control groups. Statistical analysis of absolute organ weights, organ to body weight ratios and organ to brain weight ratios compared favorably across the test and control groups, and were within the range of expected values for albino rats of this age and strain. Histopathological examination of organs and tissue taken from high-dose animals and controls at 24 months revealed no treatment-related lesions. Any lesions noted were from those of naturally-occurring diseases, and were noted in both populations. Microscopic examination of suspect lesions from all sacrificed animals and also those that died during the study. No differences were noted between test and control rats as to the organ system involved, type or classification of neoplasms..

Reliability: (1) valid without restriction
GLP study, meets generally accepted scientific standards, well documented and acceptable for assessment

Flag: Critical study for SIDS endpoint

20-NOV-2001 (51) (52)

Species: rat Sex: male/female
Strain: no data
Route of admin.: oral feed
Exposure period: after 12 months interim sacrifice (no further data)
Frequency of treatment: daily
Post. obs. period: no data
Doses: 50, 250 or 1500 ppm (4, 20 or 120 mg/kg bw/d)
Control Group: yes
Method:
Year: GLP: no data
Test substance: other TS: Santoflex 13
Remark: The NOEL for chronic toxicity was determined to be 50 ppm, and a NOEL for oncogenic effects was determined to be at least 1500 ppm
Result: decreased body weights in mid- and high-exposure females and high-exposure males; various hematological changes in mid- and high-exposure females and high-exposure males; some high-exposure male and female serum chemistry alterations (increased cholesterol, total protein, globulin and calcium); absolute and relative liver weights were increased for mid-exposure male rats at study termination and for high-exposure male and female rats after one year of exposure and at the end of the study; histopathological examination revealed pigment in the hepatocytes and reticuloendothelial cells of high-exposure females; mean absolute and relative kidney weights were also statistically significantly increased for high-exposure males and females compared to controls at the 12-month interim sacrifice only; a slight increase in the severity but not the incidence of chronic nephropathy was noted for high-expo-

sure males and females compared to controls at both interim and terminal sacrifice periods; high exposure males demonstrated increased absolute and relative spleen weights compared to controls at the 12-month exposure period only; neoplastic findings were similar between control and Santoflex 13-treated animals
Source: MonsantoBayer AG Leverkusen
31-MAY-1994 (53)

Species: rat Sex: no data
Strain:
Route of admin.: gavage
Exposure period: 24 days
Frequency of treatment: once a day
Post. obs. period: no data
Doses: 250 mg/kg b.w./day for the first 4 days, thereafter being increased 50 % every 5 days, no further data available
Control Group: yes
Method:
Year: GLP:
Test substance:
Result: no death, body weight gain within the normal range, increased oxygen consumption, suppression of the central nervous system and of the synthezising function of the liver (content of hippuric acid in a 24 h urine sample was decreased), decreased ascorbic acid content in the liver
Source: Bayer AG Leverkusen
08-DEC-1992 (30)

5.5 Genetic Toxicity 'in Vitro'

Type: Ames test
System of testing: Salmonella typhimurium TA-1535 TA-1537 TA-1538 TA-98 TA-100
Concentration: 0.001, 0.01, 0.1, 1.0 and 5.0 micrograms/plate
Cytotoxic Conc.:
Metabolic activation: with and without
Result: negative
Method: other: Ames Plate Test (Overlay method) 1975; OECD 471 equivalent
Year: GLP: yes
Test substance: other TS: 6PPD #BIO76-277, purity: >96%
Remark: Stock solutions prepared in DMSO. No evidence of mutagenic activity in any assay conducted with or without activation using the S-9 homogenate from Arochlor-induced rat livers.
Reliability: (1) valid without restriction
GLP guideline study
Flag: Critical study for SIDS endpoint
20-NOV-2001 (54)

Type: Ames test
System of testing: Salmonella typhimurium TA1535, TA1537, TA1538, TA98, TA100
Concentration: 0.167, 0.500, 1.67, 5.00, 16.7 and 50.0 micrograms/plate
Cytotoxic Conc.: Precipitation conc: >500 micrograms/plate
Metabolic activation:
Result:
Method: other: Revised Method for the Salmonella Mutagenicity Test (1983), Maron, D.M. and Ames, B.N.
Year: GLP: yes
Test substance: other TS: 6PPD purple solid #4065461, purity: >96%
Remark: Stock solutions prepared in DMSO. All tester strains contained a uvrB deletion mutation and an rfa mutation. Cytotoxicity of test article was determined in a screening test on duplicate cultures of TA1538 and TA100 in the absence of S9. In the definitive assay, inhibited growth was observed at concentrations >5.00, both with and without S9 activation. Revertant frequencies for all doses, in all strains, both with and without metabolic activation were equal to or less than those of controls. Results for the test article were negative under the test conditions.
Reliability: (1) valid without restriction
GLP study, meets generally accepted scientific standards, well documented and acceptable for assessment
Flag: Critical study for SIDS endpoint
20-NOV-2001 (55)

Type: Gene mutation in Saccharomyces cerevisiae
System of testing: Saccharomyces cerevisiae D4
Concentration: 0.001, 0.01, 0.1, 1.0 and 5.0 micrograms/plate
Cytotoxic Conc.:
Metabolic activation: with and without
Result: negative
Method: other: Ames Plate Test (Overlay method) 1975; OECD 471 equivalent
Year: GLP: yes
Test substance: other TS: 6PPD #BIO76-277, purity: >96%
Remark: Stock solutions prepared in DMSO. No evidence of mutagenic activity in any assay conducted with or without activation using the S-9 homogenate from Arochlor-induced rat livers.
Reliability: (1) valid without restriction
GLP guideline study
Flag: Critical study for SIDS endpoint
20-NOV-2001 (54)

Type: Mammalian cell gene mutation assay
System of testing: Mouse lymphoma cells (L5178Y TK+/-)
Concentration: 0.25, 0.5, 1.0, 2.0, 4.0 or 8.0 micrograms/ml
Cytotoxic Conc.: With metabolic activation: 33 micrograms/ml; Without metabolic activation: > 4 micrograms/ml
Metabolic activation: with and without
Result: negative
Method: other: OECD 476 equivalent
Year: GLP: yes
Test substance: other TS: 6PPD/CP22423 , purity: >96%
Remark: Negative for ability to induce forward mutations at the TK locus.
Reliability: (1) valid without restriction
GLP study, meets generally accepted scientific standards, well documented and acceptable for assessment
Flag: Critical study for SIDS endpoint
20-NOV-2001 (56)

Type: Mammalian cell gene mutation assay
System of testing: Chinese hamster ovary cells (CHO/HGPRT)
Concentration: up to 5 ug/ml without S9-mix, up to 15 ug/ml with S9-mix
Cytotoxic Conc.: With metabolic activation: 9 micrograms/ml; Without metabolic activation: 4 micrograms/ml; Solubility limit of test article = 333 micrograms/ml
Metabolic activation: with and without
Result: negative
Method: other: CHO/HGPRT Mutation Assay (1979) Hsie, et.al.
Year: GLP: yes
Test substance: other TS: 6PPD purple pellets lot# KH04, purity: 96%
Remark: 6PPD was tested in CHO cells at different S9 concentrations up up to cytotoxic concentrations in two range-finding, one initial and one confirmatory experiments. The cytoxicity of the test article decreased with increasing S9 concentrations. No statistically significant mutagenicity was observed. 6PPD is not considered mutagenic to CHO cells under test conditions.
Reliability: (1) valid without restriction
Flag: Critical study for SIDS endpoint
20-NOV-2001 (57)

Type: Unscheduled DNA synthesis
System of testing: primary rat hepatocytes
Concentration: 0.1, 0.5, 1, 5, 10, 50, 100, 500, 1000 and 5000 micrograms/ml
Cytotoxic Conc.: 50 micrograms/ml
Metabolic activation: without
Result: negative
Method: other: Williams, G.M., 1977. Detection of Chemical Carcinogens by Unscheduled DNA Synthesis in Rat Liver Primary Cell Cultures
Year: GLP: yes
Test substance: other TS: 6PPD purple pastilles Lot# KH04-70, purity: 96%
Remark: Reagent grade Acetone (1%) as solvent. 6PPD was examined for genotoxicity in the UDS Assay. Primary rat lever cell cultures used for both the preliminary and replicate experiments were derived from the livers of two adult male Fischer-344 rats (13 and 18 weeks old, respectively).
Quantitative autoradiographic grain-counting was performed using an ARTEK Model 980 colony counter interfaced with a Zeiss Universal Microscope via an ARTEK TV camera. Data were fed directly to a VAX computer. Cytotoxicity was observed at concentrations of 50 micrograms/ml and above in both the preliminary and replicate experiments. UDS was measured at concentrations of the test article between 0.1 and 10 micrograms/ml in both experiments. The net grain counts were negative at each concentration of the test compound, in the solvent control, and in the medium control, in contrast to the strong positive response produced in both experiments by the positive control. These results indicate that 6PPD is not a genotoxic agent under the conditions of the in vitro rat hepatocyte DNA repair assay.
Reliability: (1) valid without restriction
GLP study, meets generally accepted scientific standards, well documented and acceptable for assessment
Flag: Critical study for SIDS endpoint
20-NOV-2001 (58)

Type: Cytogenetic assay
System of testing: Chinese hamster ovary cells (CHO)
Concentration:
Cytotoxic Conc.:
Metabolic activation: no data
Result: negative
Method: other: chromosomal aberrations
Year: GLP:
Test substance:
Remark: no further data available
Source: Bayer AG Leverkusen
20-NOV-2001 (59)

Type: Cytogenetic assay
System of testing: Chinese hamster ovary cells
Concentration: up to 15 ug/ml
Cytotoxic Conc.:
Metabolic activation: no data
Result:
Method:
Year: GLP: no data
Test substance: other TS: Santoflex 13
Remark: effects: Santoflex 13 showed a marginal potential for inducing chromosomal aberrations
type: chromosomal aberration assay
Source: MonsantoBayer AG Leverkusen
20-NOV-2001 (60)

Type: Ames test
System of testing: Salmonella typhimurium TA 98, TA 100, TA 1535, TA 1537, TA 1538
Concentration: up to 1000 ug/plate
Cytotoxic Conc.:
Metabolic activation: with and without
Result: negative
Method: other: Ames Salmonella/Microsome (EPA/OECD)
Year: 1984 GLP:
Test substance: other TS: Flexzone 7F
Source: Bayer AG Leverkusen
Reliability: (2) valid with restrictions
21-OCT-1999 (61)

Type: Ames test
System of testing: Salmonella typhimurium TA 98, TA 100, TA 1535, TA 1537, TA 1538
Concentration:
Cytotoxic Conc.:
Metabolic activation: with and without
Result: negative
Method:
Year: GLP:
Test substance:
Remark: no further data available
Source: Bayer AG Leverkusen
08-DEC-1992 (62)

Type: Ames test
System of testing: Salmonella typhimurium TA 98, TA 100, TA 1535, TA 1537
Concentration: up to 200 ug/plate
Cytotoxic Conc.:
Metabolic activation: with and without
Result: negative
Method:
Year: GLP:
Test substance:
Source: Bayer AG Leverkusen
08-DEC-1992 (63)

Type: Ames test
System of testing: Salmonella typhimurium
Concentration:
Cytotoxic Conc.:
Metabolic activation:
Result: negative
Method:
Year: GLP:
Test substance:
Remark: no further data available
Source: Bayer AG Leverkusen
08-DEC-1992 (64) (65) (66)

Type: Ames test
System of testing: Salmonella typhimurium (no further data)
Concentration: up to 500 ug/plate
Cytotoxic Conc.:
Metabolic activation: with and without
Result: negative
Method:
Year: GLP: no data
Test substance: other TS: Santoflex 13
Source: MonsantoBayer AG Leverkusen
31-MAY-1994 (67)

Type: Mammalian cell gene mutation assay
System of testing: Chinese hamster ovary cells (CHO/HGPRT)
Concentration: up to 0.6 ug/ml without S-9 mix, up to 55 ug/ml with S-9 mix
Cytotoxic Conc.:
Metabolic activation: with and without
Result: negative
Method:
Year: GLP:
Test substance:
Source: Bayer AG Leverkusen
08-DEC-1992 (68)

Type: Mitotic recombination in Saccharomyces cerevisiae
System of testing: Saccharomyces cerevisiae D4
Concentration: no data
Cytotoxic Conc.:
Metabolic activation: no data
Result: negative
Method:
Year: GLP: no data
Test substance: other TS: Santoflex 13
Source: MonsantoBayer AG Leverkusen
31-MAY-1994 (69) (70)

Type: Sister chromatid exchange assay
System of testing: Chinese hamster ovary cells (CHO)
Concentration:
Cytotoxic Conc.:
Metabolic activation: no data
Result: negative
Method:
Year: GLP:
Test substance:
Remark: no further data available
Source: Bayer AG Leverkusen
08-DEC-1992 (59)

Type: Unscheduled DNA synthesis
System of testing: primary rat hepatocyte
Concentration: up to 1000 ug/well
Cytotoxic Conc.:
Metabolic activation: without
Result: negative
Method:
Year: GLP:
Test substance:
Source: Bayer AG Leverkusen
08-DEC-1992 (71)

Type: Unscheduled DNA synthesis
System of testing: primary rat hepatocytes
Concentration: up to 1000 ug/ml
Cytotoxic Conc.:
Metabolic activation:
Result: negative
Method:
Year: GLP: no data
Test substance: other TS: Flexzone 7F
Source: MonsantoBayer AG Leverkusen
31-MAY-1994 (72)

5.6 Genetic Toxicity 'in Vivo'

Type: Cytogenetic assay
Species: rat Sex: male/female
Strain: Sprague-Dawley
Route of admin.: gavage
Exposure period: 6, 18 and 30 hours
Doses: 1000 mg/kg bw
Result: negative
Method: other: EPA Health Effects Test Guidelines EPA 560/6-82-09
Year: 1984 GLP: yes
Test substance: other TS: 6PPD Lot# KJ09-165, purity: 96%
Remark: Not clastogenic under test conditions. Mild to severe pharmacotoxic effects observed in test animals indicated that the test article was administered near the maximum tolerated dose.
Reliability: (1) valid without restriction
GLP study, meets generally accepted scientific standards, well documented and acceptable for assessment
Flag: Critical study for SIDS endpoint
20-NOV-2001 (73)

Type: Cytogenetic assay
Species: mouse Sex: male
Strain:
Route of admin.: i.p.
Exposure period: twice within 24 hours
Doses: 100 and 200 mg/kg bw
Result: negative
Method: other: no data
Year: GLP: no data
Test substance: no data
Result: no induction of chromosomal abnormalities
Source: Bayer AG Leverkusen
20-NOV-2001 (74)

Type: Micronucleus assay
Species: mouse Sex: male/female
Strain: CD-1
Route of admin.: i.p.
Exposure period: 1 day
Doses: 1000 mg/kg
Result: negative
Method:
Year: GLP:
Test substance:
Remark: clinical signs were assessed
Result: no increased number of micronucleated erythrocytes
Source: Bayer AG Leverkusen
20-NOV-2001 (75) (76)

Type: Micronucleus assay
Species: mouse Sex: male
Strain:
Route of admin.: i.p.
Exposure period: twice within 24 hours
Doses: 100, 150 and 200 mg/kg bw
Result: negative
Method: other: no data
Year: GLP: no data
Test substance: no data
Result: no induction of micronucleated erythrocytes in bone marrow
Source: Bayer AG Leverkusen
20-NOV-2001 (74)

5.7 Carcinogenicity

Species:	rat Sex: male/female
Strain:	other: Charles river CD
Route of admin.:	oral feed
Exposure period:	24 months
Frequency of treatment:	daily
Post. obs. period:	no
Doses:	100, 300, 1000 ppm (8, 23, 75 mg/kg b.w./day)
Result:	
Control Group:	yes, concurrent no treatment
Method:	
Year:	GLP:
Test substance:	
Remark:	the calculation of the dose levels is based on 1 ppm corresponds to 0.075 mg/kg b.w.; 50 male and female rats per group
Result:	the number and type of neoplastic and nonneoplastic lesions were comparable between groups
Source:	Bayer AG Leverkusen

08-DEC-1992 (77)

Species:	rat Sex: male/female
Strain:	no data
Route of admin.:	oral feed
Exposure period:	after 12 months interim sacrifice (no further data)
Frequency of treatment:	daily
Post. obs. period:	no data
Doses:	50, 250 or 1500 ppm (4, 20 or 120 mg/kg bw/d)
Result:	
Control Group:	yes
Method:	
Year:	GLP: no data
Test substance:	other TS: Santoflex 13
Remark:	a NOEL for oncogenic effects was determined to be at least 1500 ppm
Result:	neoplastic findings were similar between control and Santoflex 13-treated animals (no further data)
Source:	MonsantoBayer AG Leverkusen

31-MAY-1994 (53)

Species: other: (see remarks) Sex:
Strain:
Route of admin.:
Exposure period:
Frequency of treatment:
Post. obs. period:
Doses:
Result:
Control Group:
Method:
Year: GLP: yes
Test substance:
Remark: BALB/3T3 cells; cell transformation assay under nonactivation conditions
Result: negative
Source: Bayer AG Leverkusen
08-DEC-1992 (78)

5.8 Toxicity to Reproduction

Type: Fertility
Species: rat Sex: male/female
Strain: Sprague-Dawley
Route of admin.: gavage
Exposure Period: Males: 42 or 49 days, Females: 14 days prior to mating through Day 7 of gestation
Frequency of treatment: daily
Premating Exposure Period
male: 28 days.
female: 14 days
Duration of test:
Doses: 0, 40, 200 or 1000 ppm
Control Group: yes, concurrent vehicle
NOAEL Parental: > 1000 ppm
NOAEL F1 Offspr.: > 1000 ppm
Method: other: Fertility Study and Early Embrionic Development to Implantation in Rats, DRL
Year: 1998 GLP: no data
Test substance: other TS: CD-13, purity >98%
Remark: The test article is being evaluated as a new diagnostic drug of Helicobacter pylori. To this end, several reproductive and developmental toxicity studies have been conducted recently by this laboratory. All reports published to date have indicated that there are no reproductive, developmental or fetotoxic effects of this chemical under the test conditions.
Result: Groups of male and female rats were dosed with the test article at the above levels prior to mating. Males and females from the same dose levels were paired. Animals were observed for body weight, weight gain, food consumption, appearance, behavior, copulation index and fertility index during the life phase of the study. Mated females were

sacrificed on Day 14 of gestation and the fetuses removed via Cesarean Section. Fetuses were weighed, sexed and examined for external, skeletal and soft tissue anomalies as well as developmental variation
General parental toxicity: All animals survived until planned sacrifice. There were no effects of treatment observed on mean body weight, weight gain, appearance, behavior, physical viability, copulation index or fertility index. There were no remarkable findings in gross necropsy or organ weights.
Toxicity to offspring: The number of corpora lutea and implantations, implantation rate, fetal mortality, and number of live fetuses were not affected by the test article.

Reliability: (2) valid with restrictions
Meets generally accepted scientific standards, well documented and acceptable for assessment
Flag: Critical study for SIDS endpoint
20-NOV-2001 (79)

Type: other: Three generation study
Species: rat Sex: male/female
Strain: other: Charles river CD
Route of admin.: oral feed
Exposure Period: for three successive generations
Frequency of treatment: daily
Duration of test:
Doses: 100, 300, 1000 ppm (8, 23, 75 mg/kg b.w./day)
Control Group: yes, concurrent no treatment
NOAEL Parental: 10 ppm
Method: other: the F0-generation received the test compound for 11 weeks before mating and during mating, gestation and lactation for two successive litters (F1a, F1b)
Year: GLP:
Test substance:
Remark: the calculation of the dose levels is based on 1 ppm corresponds to 0.075 mg/kg b.w.
Result: F0-generation: no effect on fertility, no effect on behaviour, reduced body weight gain at the mid and high dose levels, no substance-related histopathological effects
F1-generation, F2-generation, F3-generation: no effect on fertility, no effect on behaviour, no substance-related histopathological effects
Source: Bayer AG Leverkusen
Reliability: (2) valid with restrictions
Flag: Critical study for SIDS endpoint
20-NOV-2001 (80) (52)

Type: other: rangefinding study
Species: rat Sex: female
Strain: no data
Route of admin.: gavage
Exposure Period: gestation days 6 to 15
Frequency of treatment: daily
Duration of test:
Doses: 100, 300, 600, 1000 or 2000 mg/kg bw/d
Control Group: yes
Method:
Year: GLP: no data
Test substance: other TS: Santoflex 13
Result: excessive toxicity was noted at 600 mg/kg bw/d and above; intrauterine survival was not affected by treatment at 100 or 300 mg/kg bw/d
Source: MonsantoBayer AG Leverkusen
31-MAY-1994 (81)

5.9 Developmental Toxicity/Teratogenicity

Species: rat Sex: female
Strain: Sprague-Dawley
Route of admin.: gavage
Exposure period: days 6-15 of gestation
Frequency of treatment: daily
Duration of test: 20 days
Doses: 0, 50, 100 or 250 mg/kg bw/d
Control Group: yes, concurrent vehicle
NOAEL Maternalt.: = 50 mg/kg bw
NOAEL Teratogen.: > 250 mg/kg bw
Method: other: Teratology - Principles and Techniques, J.G. Wilson 1965
Year: GLP: yes
Test substance: other TS: 6PPD Lot# KE-10-143 purity: >97%
Remark: Four groups of 25 bred female rats were dosed with the test article at 0, 50, 100 and 250 mg/kg/body weight. Dosages were determined in a preceding range-finding study. Survival was 100% in all groups. Throughout gestation, all animals were observed 2x/day for appearance, behavior, body weight and food consumption. On Day 20, all test animals were sacrificed and the fetuses removed via Cesarian Section. Fetuses were weighed, sexed and examined for external, skeletal and soft tissue anomalies as well as developmental variation.
This was a follow-up study to a range-finding study (Monsanto WI-85-304) that noted excessive maternal toxicity at dose levels of 2000, 1000 and 600 mg/kg/day, with clinical signs of toxicity in the 300 mg/kg/day group. Intrauterine survival was not affected at the 100 and 300 mg/kg/day dose levels.
Result: Maternal general toxicity: Clinical signs noted in the Mid- to High-dose groups included salivation prior to dosing, soft stool, diarrhea and green fecal discoloration. Maternal body weights and weight gain were comparable in all groups. No

morphopathological changes which could be attributed to the test article were observed in any of the treated animals
Pregnancy/litter data: No abortions or premature deliveries occurred in any test group.
Foetal data: No differences that could be associated with the test article were observed between the control group and the treated groups with respect to number of viable fetuses, early and late resorptions, fetal sex ratios or fetal weights. The types of malformations and the frequency of such mutations occurring during this study were not those indicative of a teratogenic response. There was a small, non-statistically significant increase in the incidence and number of skeletal variations in the treated groups. However, these were judged to be common developmental variations of this species and have been observed to occur with similar incidence in the historical data.
Not teratogenic or embryo/fetotoxic under test conditions.

Reliability: (1) valid without restriction
GLP study, meets generally accepted scientific standards, well documented and acceptable for assessment

Flag: Critical study for SIDS endpoint

20-NOV-2001 (82)

Species: rabbit Sex: female
Strain: other: New Zealand
Route of admin.: oral unspecified
Exposure period: gestation day 6 through day 18 inclusive
Frequency of treatment: once a day
Duration of test: post observation: sacrifice on gestation day 29
Doses: 10, 30 mg/kg b.w./day
Control Group: other: yes, empty gelatin capsules
NOAEL Maternalt.: 30 mg/kg bw
Method:
Year: GLP:
Test substance: other TS: Santoflex 13
Remark: in a pilot study 100 and 300 mg/kg b.w./day caused maternal toxicity
Result: maternal body weight loss and mortality comparable to the controls, no treatment related gross lesions were noted at necropsy; a slight increase in the number of resorption sites per 100 implantation sites for the 30 mg/kg b.w. group (38.6 %) when compared to the controls (31.4 %), the number of live young per 100 implantation sites for the 10 mg/kg b.w. group (48.3 %) and for the 30 mg/kg b.w. group (38.6 %) were moderately decreased when compared to the controls (68.6 %); no increase in the incidence of external, visceral and skeletal abnormalities
Source: Bayer AG Leverkusen

20-NOV-2001 (83)

Species: Sex:
Strain:
Route of admin.:
Exposure period:
Frequency of treatment:
Duration of test:
Doses:
Control Group:
Method: other: test compounds were tested for embryotoxicity and induction of malformations in three-day chicken embryos
Year: GLP:
Test substance:
Result: slight effects
Source: Bayer AG Leverkusen
08-DEC-1992 (84) (85)

5.10 Other Relevant Information

Type: other
Remark: A comprehensive description of the toxicity profile is available in the BUA-Report
Source: Bayer AG Leverkusen
12-NOV-1998 (86)

Type:
Remark: Revision date: August, 1998
Source: Bayer AG Leverkusen
17-AUG-1998

5.11 Experience with Human Exposure

Memo: Occupational eczema study - 6PPD and IPPD exposures
Remark: Cross sensitization in rubber workers exposed to various members of the PPD family have been reported. Anecdotal evidence suggests that this class of compounds has a high potential for skin sensitization with prolonged and repeated exposures of sensitive individuals.
20-NOV-2001 (87)

Remark: In the rubber industry 6PPD was detected in the urine of 6PPD exposed workers
Source: Bayer AG Leverkusen
08-DEC-1992 (88)

Remark: analytical methods for the determination of the trace levels of 6PPD in human urine are described (in the publication of Pavan et. al the abbreviation 6PPD is used however the substance is called N-(2,3-dimethylpropyl)-N-phenyl-1,4-benzenediamine with the CAS-No. 739-24-8)
Source: Bayer AG Leverkusen
08-DEC-1992 (89) (90)

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(38) Monsanto data, Project No. SH-64-6, Experiment No. 16-91, Comparison of n-Hexyl Analog with Santoflex 13, March 23, 1964

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7.1 End Point Summary

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7.2 Hazard Summary

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7.3 Risk Assessment

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